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Original Communications

A PRACTICAL METHOD FOR THE REDUCTION OF PLASMA CHOLESTEROL IN MAN

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IN A recently published "arm-chair" study, certain factors possibly contributing to the pathogenesis of atherosclerosis were pointed out.[1] While still unproved, there is experimental evidence that trace metals, pyridoxal phosphate, and unsaturated fatty acids may be involved in a biochemically interrelated fashion, either in the production of the lesions or in the synthesis of cholesterol and fatty acids. Furthermore, calcium disodium ethylenediamine tetraacetate (Calcium EDTA), a nonmetabolized chelating agent, has been found to lower plasma cholesterol in man quite dramatically when given intravenously[2]; because this compound is excreted in toto unchanged,[3,4] presumably its effect is the result of removal of an essential or nonessential trace metal with metabolic activity. Certain vegetable oils with high iodine numbers have been shown to lower plasma cholesterol in man[5-8] even when given as the major source of calories; other vegetable oils and saturated animal fats act in an opposite manner.[5-9]

The plasma cholesterol levels of healthy human beings in certain parts of the world may be normally much lower than those usually found in Western countries. For example, in India, ranges of 120 to 160 mg. per 100 ml. of blood were normal[10]; in Israeli Yemenite Jews the mean values for men between 35 and 44 years of age

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TABLE I. COMPOSITION OF SOME COMMON VEGETABLE FATS ALTERING PLASMA CHOLESTEROL IN MAN (PARTLY AFTER DEUEL[13] AND ECKEY[37])

	FATTY ACIDS (PER CENT)							
	OLEIC	LINOLEIC	LINOLENIC	ARACHIDONIC	SQUALENE (MG. %)	I_2 NO.	REF.	REMARKS
Fats lowering levels								
Soybean oil	25	53	8	0.05	12	131–133	(7)	Analysis by Glidden Co.
Corn oil	21–49	34–61	0–0.6	0	28	103–129	(5–8)	Composition varies
Sunflower seed oil	14–43	44–75	0.1*	0	12	113–142	(26)	Composition varies
Some nuts	18–35	38–73	2.9–3.2	0	—	—	(34)	Walnut, beechnut, etc.
Fats raising or not changing levels								
Peanut oil	42–71	13–33	0	0	27	90–96	(7)	Composition varies
Cottonseed oil	19–36	34–56	0	0	8	90–110	(9)	Composition varies[35]
Olive oil	64–86	4–15	0	0	383	79–90	(9)	Composition varies
Coconut oil	5–8	1–2.6	0	0	2	6–9	(7, 9)	Short-chain fatty acids

*In African variety, probably not others.

Note: 1. The unsaturated fatty acid content of vegetable oils varies according to climate, rainfall, soil, variety of seed, and other factors.
2. Bronte-Stewart et al.[26] showed protective effects of olive oil in *hypocholesterolemic* Bantu. Peanut oil had a slight effect in a European.
3. Keys'[9] patients were on a low fat diet.

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were 146 ± 28.4 mg. per 100 ml.[11] and for men in the next decade 160 ± 31.1 mg. In New York City, comparable levels were 214 ± 82 and 220 ± 26 mg.[12]

While it is yet unproved that a lowered plasma cholesterol will induce regression of some of the lesions of atherosclerosis, most students of the subject believe that the disease is common when cholesterol is high and uncommon when it is low. The method here reported is a preliminary approach to reducing high plasma cholesterol values to lower levels approaching those reported in Indians and Yemenite Jews in an attempt to observe changes in the atherosclerotic process over the long term. Although low "normal" values were not attained in all individuals, the changes were significant enough to warrant use of the method, which does not impose severe restrictions.

LOGIC OF METHOD

There are three phases to the approach, two backed by some experimental data and the third theoretical.

1. *Diet.*—The vegetable oils shown to lower plasma cholesterol in man contain linolenic acid; those raising it do not (Table I). Therefore, linolenic acid was provided in the diet as a constituent of soybean oil (8 per cent linolenic) or corn oil (0.5 per cent linolenic).

Since the high animal fat (saturated fatty acid) intake of Western countries is believed to be a factor in atherogenesis, certain foods high in fat were restricted. Fats of milk and milk products, of known cholesterol raising properties,[5,6] and highly saturated animal fats from pork were restricted, as the practice of fattening cattle and pigs before slaughter with a high carbohydrate diet lays down a hard fat.[13]

2. *Metal Chelation.*—Plasma cholesterol in man can be lowered in some patients by oral calcium EDTA.*[2,14] Certain transitional metals affect hepatic synthesis of cholesterol and fatty acids, chromium and manganese increasing it and vanadium depressing it.[15] Bernheim and Bernheim[16] have shown that vanadium acts to desaturate fatty acids on phospholipids and then, by another mechanism, oxidizes the double bond, manganese opposing this reaction; they postulate a vanadium-manganese antagonism in hepatic metabolism of phospholipids. Furthermore, Curran[17] has shown that the cholesterol and fatty acid content of aortas of rabbits fed cholesterol was less when vanadyl sulfate was added to the diet. Therefore, the chelating agent calcium EDTA was given orally.

3. *Vitamin* B_6.—Aside from its function as cotransaminase and codecarboxylase, this coenzyme apparently is concerned with desaturation of certain partly unsaturated fatty acids, promoting the metabolism of linoleate to arachidonate and linolenate to hexaenoate.[18] Furthermore, deficiency of this vitamin produces the subintimal lesions in monkeys characteristic of early atheromata.[19,20] While cholesterolysis by vitamin B_6 has not been shown, deficient monkeys exhibit higher levels when fed the sterol than do normal controls.[21] Therefore, an adequate intake of vitamin B_6 was provided.

*In eleven patients showing a mean control value of plasma cholesterol of 233 mg. per 100 ml., levels fell 55 ± 46.03 mg. in 4 to 44 months while each was taking 1.0 Gm. daily of calcium EDTA, a change of 24 per cent.

TABLE II. EFFECT OF REGIMEN ON PLASMA CHOLESTEROL (MILLIGRAM PER CENT)

PATIENT	AGE SEX	PRETREATMENT			2 MONTHS	4 MONTHS	RANGE AFTER 3 MONTHS	NUMBER OF SAMPLES	DIAGNOSIS AND REMARKS
		RANGE	MEAN	NO. SAMPLES					
D. Lik.	56 ♀	481–624	552	6	377	366	366–422	3	Xanthomytosis
R. Ber.	53 ♀	299–323	312	2	279	298	298–321	4	Hypercholesterolemia
C. Cru.	62 ♂	260–300	280	3	236	200	112–237	9	Hypertension
L. Bat.	62 ♀	256–300	280	3	183	250	241–250	7	Atherosclerosis
E. Sti.	70 ♀	276–278	277	2	151	216	216–227	12	Atherosclerosis
G. Boa.	55 ♂	233–272	261	4	155	137	137–272	8	Hypertension
M. Bro.	72 ♀	245–276	257	4	237	172	172–184	3	Atherosclerosis
G. Hir.	46 ♂	238–262	250	3	185			1	Angina pectoris
D. Blu.	49 ♂	219–295	244	4	179	204	176–204	6	Hypertension
B. McD.	52 ♂	204–278	241	2	145	128	105–156	8	Peripheral vasc. dis.
H. Sch.	49 ♂	237–244	240	2	146	168	146–172	12	Normal
E. Shr.	49 ♂	228–249	239	3	119	232	119–232	4	Angina pectoris
C. Gri.	57 ♂	210–253	234	3	206	181	171–201	6	Hypertension and Leriche's syndrome
S. Mat.	61 ♀	207–240	224	2	146	198	190–234	6	Hypertension
E. Fri.	69 ♀	217–231	224	2	128	185	161–196	3	Parkinsonism
G. Nes.	45 ♂	213–234	223	4	178	180	159–197	7	Hypertension
K. Sch.	59 ♂	200–217	212	4	120	141	117–154	8	Hypertension
A. Bla.	48 ♂	162–259	209	4	216	287	287	4	Hypertension
A. Han.	60 ♀	174–207	194	3	168	171	171–200	5	Mild hypertension
R. She.	55 ♂	162–176	170	5	121	131	114–140	8	Mild hypertension
Mean			257		181	200			
Change and S. D.					76 ± 40.62	62 ± 42.77			

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METHODS

Twenty ambulatory patients were given a diet in which the short-chain saturated fatty acids in dairy products and the long-chain saturated fatty acids in hydrogenated vegetable oils were avoided and excess animal fat on meat and meat products was reduced in so far as practicable; pork products were avoided entirely. Fish was allowed ad libitum. The caloric equivalent in fat was thus reduced from the usual 40 per cent to less than 20 per cent. Such a fairly liberal diet was not found to affect plasma cholesterol in man very much.

An adequate intake of vegetable fat containing linolenic acid was provided by the use of soybean oil for cooking and salad dressings (8 per cent linolenate, range 3 to 11 per cent) or corn oil (0.5 per cent linolenate). Corn oil was used in the initial studies, soybean oil being substituted exclusively later. Other possible sources of linolenate are in linseed (40 to 53 per cent), millet seed (6 to 8 per cent), walnut (3.2 per cent), and beechnut (2.9 per cent) oils, most of which are not readily available as foods. An attempt was made to provide 0.2 to 0.5 Gm. linolenic acid per day. In all oils containing linolenate, linoleate is also present in large quantities.

Calcium disodium ethylenediamine tetraacetate (Calcium Disodium Versenate), 1.0 Gm. per day orally, was given either in single or divided doses. This material can be recovered in feces for several days after a single dose.[4] Pyridoxine hydrochloride, 10 mg. daily, was given orally.

Plasma cholesterol levels were measured before and at biweekly or monthly intervals after initiation of the regimen, by the method of Saifer and Kammerer,[22] in the routine hospital laboratory. No restriction of activity on the part of the patients was imposed other than those required by ischemic manifestations in myocardium or legs.

RESULTS

The results are shown in Table II. Nine of the 20 patients eventually exhibited plasma cholesterol concentrations comparable to the Oriental "normal" ranges; in three, changes were insignificant. Mean cholesterol concentrations fell by 29 per cent in two months but were only 20 per cent lower, after four months, than the initial value of 258 mg. per 100 ml. plasma. Values were obtained at the exact times shown.

No adverse symptoms appeared. The frequency of anginal attacks in five individuals was claimed by them to be considerably lessened; one individual with several attacks a day, who had previously suffered from a severe myocardial infarction, claimed complete relief. No changes were noticed by two patients suffering from previously progressive intermittent claudication. Laboratory evidence of hepatocellular damage was not observed in this or in previous studies using calcium EDTA for as long as a year.

DISCUSSION

The regimen apparently offers a simple, practical, and not too restrictive diet for ambulatory patients taking most of their meals at home, but it is almost

impossible to apply to those eating in restaurants or at soda fountains. Patient education was, however, essential; in several instances directions were misunderstood or individuals became tired of their diets, with either failure of plasma levels to fall, or actual rise. An analysis of the care with which patients took their diets revealed that the nine achieving low values were in general the most careful. On the other hand, the diet without chelating agent or vitamin B_6 was usually not associated with profound falls. This discrepancy remains to be explained.

While there is a possibility that the changes in plasma cholesterol were spontaneous and uninfluenced by the regimen, as Wilkinson and his associates have pointed out,[23] this explanation is unlikely, for the values exhibited by many individuals were considerably lower than those which these workers found as normal fluctuations. A previous study using the identical analytical method has not impressed us with such wide downward fluctuations as were observed during this one.[2] On the other hand, a seasonal fall occurring during the winter months in a majority of patients has not been ruled out. While oral EDTA alone lowered plasma cholesterol considerably (24 per cent),[14] the patients in the present study exhibited a higher initial mean value (257 mg. per 100 ml. as opposed to 233 mg.) and the fall was numerically greater, especially in individual cases. That diet had little influence remains, however, a possibility. We have observed no chronic toxicity, especially that due to hepatic damage, in patients taking EDTA for as long as a year.

This regimen cannot be adapted readily to a "double blindfold" evaluation of its effects on ischemic symptoms. Therefore, improvement claimed by the several patients must be discounted until further data are obtained.

The hypothesis that relative hypercholesterolemia (above Oriental values) is in part a manifestation of an essential fatty acid deficiency, especially of linolenic acid, has only recently been explored. Snapper[24] suggested in 1941 that the low incidence of atherosclerosis and the high iodine numbers of the plasma lipids (mean, 156.6) in North Chinese might be the result of an adequate intake of linoleic and especially linolenic acids. Examination of the vegetable oils which have been shown to lower or raise plasma cholesterol in man strongly suggests that one common denominator is the presence or absence of linolenic acid, and not necessarily plant sterols or squalene, a precursor of cholesterol.[25] The usual American diet is obviously low in linolenic acid. There has been recent interest in the idea that unsaturated fatty acids may play a part in causing hypercholesterolemia,[26] but to our knowledge little attention has been paid to the possible role of linolenic acid.[9,36]

The use of oral EDTA was based upon the observations that this chelator, when given intravenously, lowers plasma cholesterol in man presumably by removing some trace metal active in synthesis or opposing catabolism. That certain trace metals can affect not only cholesterol synthesis (chromium, manganese, vanadium) but also partly inhibit deposition of cholesterol in the aorta of experimental animals (vanadium) has been well demonstrated by Curran.[15,17] The presence of chromium in fair quantities in the livers of American adults and stillborn children and its considerably decreased amounts in livers from adult African natives has been shown by Tipton and her associates.[27,28] EDTA given

orally is only partly (5 per cent) eliminated by the kidney; because of its high solubility and slow elimination by the feces, it presumably passes into the liver and is excreted in bile. If so, slow removal of certain trace metals from liver and intestinal contents, notably copper, zinc, nickel, cadmium, iron, lead, and chromium, might be expected when the metal was less firmly chelated to tissue than to EDTA. While the metal or metals removed in man are not known, presumably one or more are members of metalloenzyme systems concerned in cholesterol metabolism.

The use of vitamin B_6 is empirical. Theoretically this coenzyme requires a trace metal for certain of its functions[29]; it is quite possible that zinc is the essential metal on the decarboxylases of dihydroxyphenylalanine[14] and 5-hydroxytryptophane,[30-32] both pyridoxal enzymes. The Schiff base formed by pyridoxal and amino acids is a strong chelating agent.[33] Furthermore, this vitamin, being concerned with the desaturation of partly unsaturated fatty acids and converting linoleic to arachidonic and linolenic to the hexaenoic acids, appears to be necessary for the synthesis of highly unsaturated fatty acids from their precursors. Deficiency produces in monkeys subintimal lesions of the ground substance of arteries, probably in mucopolysaccharides, which appear microscopically identical to the earliest atherosclerotic lesions before lipid is deposited. Therefore, this vitamin may be involved in preventing formation of the locus for deposits of cholesterol esters. The usual American diet of processed foods may be marginal in respect to this vitamin during certain seasons of the year.[1]

These three influences on cholesterol and fatty acids appear to be interrelated biochemically; metals in synthesis of cholesterol, pyridoxal phosphate in synthesis of essential fatty acids and in arterial lesions, and essential fatty acids themselves in cholesterol transport or metabolism. Further studies are necessary to clarify their interrelationships.

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SUMMARY

A practical method has been devised to lower plasma cholesterol in ambulatory patients, based on a diet fairly low in saturated fatty acids but providing an adequate intake of linolenic acid, a metal chelator, and pyridoxine. Plasma levels fell variably but considerably in most of 20 patients. The rationale of such a regimen in metabolic terms has been discussed.

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STUDIES IN HYPERTENSION

II. Variability of Daily Blood Pressure Measurements in the Same Individuals Over a Three-Week Period

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THE well-known variability of blood pressure from day to day and throughout the day and the absence of standardized criteria for identifying early essential hypertension add materially to the difficulties of planning for a long-term study of hypertension. To determine the relationship between the levels of the blood pressure and etiologic factors associated with the onset and development of hypertension, it is necessary to establish a procedure for assuring the detection of significant changes in the levels and variability of blood pressure from one of the periodic observations to another. Before undertaking a long-term field study, therefore, a decision must be reached as to the conditions under which blood pressure readings should be made and as to the number of readings which must be taken to obtain a representative picture of the subject's blood pressure at each periodic observation. A long series of such representative readings on hypertensives and nonhypertensives in a population would provide needed information on the range of blood pressure variation under ordinary day to day living conditions and might also furnish data on important etiologic factors in hypertension.

From the review of the literature and a questionnaire addressed to a group of authorities, as reported in the first and third papers of this series,[1,2] no satisfactory answer was obtained as to what conditions of observation would provide the most accurate and consistent information on blood pressure levels and variability. The present paper is a report of an effort to devise a procedure for measuring blood pressure variability under field conditions, which, when applied at each of the periodic observations, would constitute a basis for recognizing significant changes in the status of a subject's blood pressure over time.

Study supported by funds from the Recess Commission on Hypertension, Commonwealth of Massachusetts.

TABLE I. SUMMARY OF SOME STUDIES OF DIURNAL BLOOD PRESSURE VARIATION

STUDY AND DATE	TYPE OF POPULATION STUDIED	NUMBER OF SUBJECTS	DURATION OF OBSERVATION	METHOD OF BLOOD PRESSURE MEASUREMENT	FREQUENCY OF MEASUREMENT	RANGE OF VARIATION SYSTOLIC PRESSURE (MM. HG)	SUGGESTED CORRELATES OF INCREASED BLOOD PRESSURE
Weysse and Lutz 1915[3]	Male university students	10	28½ hours	Sitting auscultatory average of 3 readings	About 15 times during waking hours	12–32	Ingestion of food
Mueller and Brown 1930[4]	Hospitalized hypertensive patients and controls	26 controls only	24 hours	Lying and sitting auscultatory	Hourly during waking hours and sleep	15–65	Gradual increase toward end of day
Diehl 1929[5]	Male university students	100	6 days	Sitting auscultatory	Twice in one day—before breakfast and before dinner	A.M. 1–39 P.M. 2–48	
Diehl and Lees 1929[6]	Male university students	100	1 hour	Sitting auscultatory	At five-minute intervals	6–46	Pressure is lower after second or third reading

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Four earlier studies are summarized in Table I. There was considerable variation in the conditions of observation in each study. Weysse and Lutz[3] studied the systolic pressure over a twenty-eight-hour period. Mueller and Brown[4] conducted a somewhat similar study on hypertensive patients and a control series. Diehl[5] made two observations daily, morning and evening, for six days, and, in a later study (Diehl and Lees[6]), blood pressure determinations were made at five-minute intervals for an hour. These studies were in agreement on one major finding, that subjects differed widely in the amount of their blood pressure variations, some exhibiting remarkable stability with only 1 or 2 mm. of change while others varied by 30 mm. or more under observation. In other respects, the results of these studies were divergent. Mueller and Brown reported higher blood pressures toward late afternoon, but this observation was not supported by others. Systolic rather than diastolic pressures were analyzed in detail in most tables.

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An important limitation in these data is that the variation of individual subjects cannot be ascertained from the published information. The reason is that the data for all subjects were grouped before analysis and the variability of the mean of the group is described. The large differences among individuals with respect to both the level and the range are not included in the analyses. It would seem more important to analyze the variation in individual subjects in order to develop standards which would permit the early recognition of essential hypertension.

Diehl and Lees had suggested that the variability in blood pressure readings during a short period of observation (one hour) appear to be as great as that noted over a six-day period. However, the published data were not consistent on this point. Should the relationship be true for periods of time longer than several days, a pattern of estimating at a single session the total range of blood pressure variability might be devised. The present field study is directed to this objective.

This study was designed to provide daily blood pressure measurements in a sample of 21 subjects over a period of a little more than three weeks. At an appointed time each examination day, subjects appeared at an examination room located near their place of work and were immediately placed in a supine position. With a mercury sphygmomanometer, an initial blood pressure reading was taken at once and subsequent ones at five-minute intervals during rest to provide six readings at each session, the last after twenty-five minutes of rest. This procedure was repeated on each subject* for seventeen weekdays, no sessions being scheduled for Saturdays and Sundays. During the test period, 15 subjects had morning, early and late afternoon sessions on one day and 7 of these had 3 sessions on two days, a total of 22 diurnal sessions. These examinations were made to furnish information on blood pressure variability throughout the day as well as from day to day.

These observations were made on a sample of subjects recruited from the headquarters staff of the Westchester County Health Department in White

*With the exception that 5 subjects missed one session, 1 missed two, 2 missed three, 1 missed four, and 1 missed five sessions.

Plains, New York. There were 10 males and 11 females distributed nearly equally among the following age groups: 21 to 35, 36 to 51, and over 51. The observations were made at the Health Department offices by two fourth year medical students associated with the Junior Health Intern Program of the New York State Department of Health.* Eleven subjects were assigned to one observer and 10 subjects to the other; each observer followed the same subjects throughout the study.

ANALYSIS OF THE RESULTS

The results are in accord with all previous observations that blood pressure varies considerably from day to day and that subjects differ markedly in the variability of their blood pressure. Table II reports the range of the systolic and diastolic blood pressure readings of each of the 21 subjects over the three-week study period.**

TABLE II. RANGES OF THE DIASTOLIC AND SYSTOLIC BLOOD PRESSURE OF 21 SUBJECTS OVER A THREE-WEEK PERIOD*

SUBJECT NUMBER	NUMBER OF OBSERVATIONS		DIASTOLIC BLOOD PRESSURES			SYSTOLIC BLOOD PRESSURES		
	SESSIONS	READINGS	MAX. (MM. HG)	MIN. (MM. HG)	RANGE (MM. HG)	MAX. (MM. HG)	MIN. (MM. HG)	RANGE (MM. HG)
1	17	102	66	54	12	110	86	24
2	16	96	90	70	20	135	106	29
3	16	96	82	68	14	122	104	18
5*	21	126	72	52	20	124	100	24
6	17	102	80	50	30	136	100	36
7	17	102	76	54	22	120	88	32
8	19	114	92	65	27	138	102	36
9	19	114	92	58	34	140	108	32
10	18	108	72	52	20	124	88	36
11	17	102	78	46	32	142	110	32
12	16	96	94	70	24	140	108	32
13	16	96	90	72	18	154	120	34
14	20	120	82	48	34	114	92	22
15	21	126	98	70	28	150	104	46
16	21	126	70	52	18	120	90	30
17	20	120	85	58	27	128	90	38
18	21	126	70	50	20	126	96	30
19	19	114	82	60	22	120	100	20
20	19	114	96	60	36	130	100	30
21	14	84	70	48	22	110	92	18
22	19	114	75	56	19	116	92	24
				Median	22		Median	30

*On this and the subsequent tables, figures for subject No. 4 are omitted since he failed to continue participating.

The subject (No. 20) exhibiting the greatest range of variability in his diastolic pressure over the study period had a high of 96 mm. Hg and a low of

*The cooperation of this department and of Dr. William C. Holla, Commissioner of Health, Westchester County Health Department, is gratefully acknowledged.

**A detailed analysis of the blood pressure readings over the study period for each subject is reported in Paper No. 3 of this series.[2]

60 mm. Hg, or a range of 36 mm. Hg. The smallest range of diastolic variability was 12 mm. Hg (Subject No. 1). The highest systolic range was 46 mm. Hg (Subject No. 15) and the lowest 18 mm. Hg (Subjects No. 3 and 21). The median diastolic range of all subjects was 22 mm. Hg and the median systolic range 30 mm. Hg.

There is *not* a strong tendency for those subjects having a high systolic range to have a high diastolic range also. The Spearman rank correlation between the systolic and diastolic ranges is +0.373.*

In view of the suggestion advanced by Diehl that variation in a single day is equal to that observed over a period of days, comparison was made between the total range observed during the entire period of observation and the variation that occurred during a single twenty-five minute session (6 readings). In Tables IIIA and IIIB, columns (2) are the differences between the highest and lowest recorded diastolic and systolic readings respectively over the entire period and columns (3) are the largest differences observed in any single session. Comparison of the two ranges, columns (4), shows that the range in diastolic pressure is always greater over the entire period than over a single session and that of the systolic in all instances except one. The differences are 5 mm. Hg or more in all except 4 diastolics and 7 systolics.

In these tables (IIIA and IIIB), column 5 indicates the number of sessions conducted on each subject and columns 6 to 10 give the distributions of sessions according to the variations noted. For example, Subject No. 20, with the widest range of diastolic variability, was studied at 19 sessions, of which 2 sessions exhibited diastolic ranges of 0 to 4 mm.; in 10 sessions the variation was between 5 and 9 mm.; in 4 sessions the variation was 10 to 14 mm.; in 2 it was 15 to 19; and in 1 it was over 20 mm. Examination of the variability in blood pressure for these subjects shows that while the maximum diastolic range at a single session was infrequently more than 10 mm. lower than the range over the entire period of study (column 4, Subjects No. 9, 14, and 20), the blood pressure variation at any *single* session clearly could not be utilized as representative of the variability that would occur during the three-week period.

During the study period, 15 subjects participated in morning, early and late afternoon sessions on one day and 7 of these did so on two days. While, as has just been seen, the range in blood pressure variability observed at a single session on a given day does not approximate the range observed over the three-week period, it is possible that the range of blood pressure variability observed in the three sessions on a single day (morning, early and late afternoon) may function as a measure of blood pressure variability over a longer period. To test this possibility, the range for each subject over the entire study period was compared with the ranges observed during three sessions conducted on a single day. In the latter case, the range is defined as the difference between the maximum and minimum of the 18 blood pressure readings taken at three sessions (Table IV).

*Perfect correlation is 1.0; under 0.6 is not considered a good correlation.

TABLE III A. RANGE OF *DIASTOLIC* BLOOD PRESSURE VARIABILITY OF 21 SUBJECTS OVER A THREE-WEEK PERIOD COMPARED WITH THE MAXIMUM DIASTOLIC RANGE EXHIBITED AT ANY SINGLE TWENTY-FIVE-MINUTE SESSION AND WITH THE DISTRIBUTION OF SINGLE SESSION DIASTOLIC RANGES OVER THE THREE-WEEK STUDY PERIOD

SUBJECT NUMBER	RANGE OVER 3-WEEK PERIOD (MM. HG)	MAX. RANGE AT SINGLE SESSION (MM. HG)	DIFFERENCE (2)-(3)	NO. OF SESSIONS	NUMBER OF SESSIONS WITH INDICATED RANGES				
					0–4 (MM. HG)	5–9 (MM. HG)	10–14 (MM. HG)	15–19 (MM. HG)	20+ (MM. HG)
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)
1	12	10	+ 2	17	6	10	1	0	0
2	20	12	+ 8	16	1	11	4	0	0
3	14	12	+ 2	16	6	9	1	0	0
5	20	17	+ 3	21	2	12	6	1	0
6	30	24	+ 6	17	3	1	11	0	2
7	22	17	+ 5	17	4	8	4	1	0
8	27	20	+ 7	19	3	8	7	0	1
9	34	22	+12	19	2	3	5	7	2
10	20	15	+ 5	18	7	8	2	1	0
11	32	15	+17	17	3	7	6	1	0
12	24	14	+10	16	3	6	7	0	0
13	18	16	+ 2	16	4	10	1	1	0
14	34	14	+20	20	6	8	6	0	0
15	28	18	+10	21	6	6	8	1	0
16	18	12	+ 6	21	12	7	2	0	0
17	27	20	+ 7	20	6	10	2	1	1
18	20	18	+ 2	21	7	1	11	2	0
19	22	14	+ 8	19	5	11	3	0	0
20	36	20	+16	19	6	3	7	2	1
21	22	14	+ 8	14	4	7	3	0	0
22	19	10	+ 9	19	5	13	1	0	0

TABLE III B. RANGE OF *SYSTOLIC* BLOOD PRESSURE VARIABILITY OF 21 SUBJECTS OVER A THREE-WEEK PERIOD COMPARED WITH THE MAXIMUM SYSTOLIC RANGE EXHIBITED AT ANY SINGLE TWENTY-FIVE-MINUTE SESSION AND WITH THE DISTRIBUTION OF SINGLE SESSION SYSTOLIC RANGES OVER THE THREE-WEEK STUDY PERIOD

SUBJECT NUMBER	RANGE OVER 3-WEEK PERIOD (MM. HG)	MAX. RANGE AT SINGLE SESSION (MM. HG)	DIFFERENCE (2)-(3)	NO. OF SESSIONS	NUMBER OF SESSIONS WITH INDICATED RANGES				
					0–4 (MM. HG)	5–9 (MM. HG)	10–14 (MM. HG)	15–19 (MM. HG)	20+ (MM. HG)
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)
1	24	18	+ 6	17	4	10	1	2	0
2	29	25	+ 4	16	1	4	8	2	1
3	18	13	+ 5	16	3	6	7	0	0
5	24	18	+ 6	21	1	6	11	3	0
6	36	20	+16	17	1	6	7	2	1
7	32	13	+19	17	0	4	13	0	0
8	36	24	+12	19	3	4	9	2	1
9	32	30	+ 2	19	0	0	9	4	6
10	36	18	+18	18	1	5	8	4	0
11	32	24	+ 8	17	3	5	5	2	2
12	32	20	+12	16	4	0	9	2	1
13	34	30	+ 4	16	1	2	8	1	4
14	22	18	+ 4	20	6	10	2	2	0
15	46	22	+24	21	2	5	9	2	3
16	30	20	+10	21	7	11	1	0	2
17	38	32	+ 6	20	5	8	4	2	1
18	30	16	+14	21	3	7	10	1	0
19	20	20	0	19	2	10	6	0	1
20	30	26	+ 4	19	2	10	4	2	1
21	18	10	+ 8	14	1	11	2	0	0
22	24	20	+ 4	19	3	9	5	1	1

TABLE IV. RANGE OF DIASTOLIC AND SYSTOLIC BLOOD PRESSURE VARIABILITY OF 21 SUBJECTS OVER A THREE-WEEK PERIOD COMPARED WITH THE RANGE OBSERVED AT THREE SESSIONS CONDUCTED ON A SINGLE DAY

SUBJECT NUMBER	DIASTOLIC BLOOD PRESSURE			SYSTOLIC BLOOD PRESSURE		
	RANGE OVER 3-WEEK PERIOD (MM. HG)	RANGE ON A SINGLE DAY 3 SESSIONS (MM. HG)	DIFFERENCE (MM. HG)	RANGE OVER 3-WEEK PERIOD (MM. HG)	RANGE ON A SINGLE DAY 3 SESSIONS (MM. HG)	DIFFERENCE (MM. HG)
1	12	10	+ 2	24	10	+14
3*	14	10	+ 4	18	13	+ 5
	14	4	+10	18	12	+ 6
5	20	7	+13	24	18	+ 6
	20	12	+ 8	24	18	+ 6
6	30	30	0	36	20	+16
7	22	10	+12	32	16	+16
	22	12	+10	32	27	+ 5
8	27	22	+ 5	36	22	+14
9	34	25	+ 9	32	32	0
14	34	12	+22	22	14	+ 8
	34	16	+18	22	16	+ 6
15	28	22	+ 6	46	24	+22
	28	18	+10	46	46	0
16	18	14	+ 4	30	12	+18
	18	6	+12	30	18	+12
17	27	20	+ 7	38	16	+22
18	20	20	0	30	24	+ 6
	20	20	0	30	16	+14
19	22	14	+ 8	20	16	+ 4
20	36	12	+24	30	16	+14
22	19	10	+ 9	24	15	+ 9

*Where there are two rows of figures for a subject, this signifies that he participated in three sessions on a single day on two days during the study period.

Table IV shows that the range of the diastolic blood pressure over the three-week period was greater than on a single day in all cases but three. For 6 of the 22 comparisons, the difference in ranges was 4 mm. Hg, or less. For the remaining 16 comparisons, the difference in ranges was 5 mm. Hg, or more.

With respect to the systolic blood pressure, the range over the three-week period was greater than the range observed in three sessions conducted on a single day in all comparisons but two. For 3 of the 22 comparisons, the difference in ranges was 4 mm. Hg, or less. However, for the remaining 19 comparisons the difference in ranges was 5 mm. Hg, or more. In none of the 22 comparisons do the diurnal diastolic *and* systolic ranges approximate the three-week range within a margin of 4 mm. Hg.

It would appear from these comparisons that a measure of the range of blood pressure variability obtained from three sessions conducted on a single day provides a satisfactory approximation of the range over a three-week period for some individuals but not for others. It is not possible, however, to distinguish those for whom it might be a suitable measure from those for whom it is not. As a result, it is not possible to adopt a diurnal measure such as has been described as an index of blood pressure variability over a period of three weeks.

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SUMMARY AND CONCLUSIONS

This paper has reported the results of a field study designed to produce an efficient measure of blood pressure variability which might be applicable under field conditions. It was undertaken preliminary to a long-term epidemiologic investigation of blood pressure in an effort to secure some pattern of blood pressure measurement which might be representative of the pressure of subjects observed at successive points in time. Six resting blood pressure measurements at five-minute intervals were taken on 21 subjects daily at the same time of day over a period of slightly more than three weeks. Similar measurements were taken three times daily (morning, early and late afternoon) on 15 subjects.

The data were analyzed in order to satisfy two objectives: one, to confirm the expectation that it is essential to incorporate a measure of blood pressure variability in the design of any long-term study of hypertension; and two, to determine whether the extent of blood pressure variation over a half-hour period or over three periods in a single day might be an accurate index of variation over a longer period of time (three weeks in this instance). The extent of the variability of the blood pressure of these subjects over the study period suggests that some measure of the range of blood pressure variability is desirable in a long-term study of hypertension. However, it was found that no single reading or group of readings obtained on a single day, as performed in this study, could serve as an index of blood pressure variability over the three-week period of this study.

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STUDIES IN HYPERTENSION

III. Analysis of Individual Blood Pressure Changes

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EVERYONE can be expected to show variability in blood pressure diurnally, from day to day, and over long periods of time. However, there is a noteworthy gap in the literature on these variations in single individuals. Most studies of blood pressure variation present data in terms of group variations. Averages, which are affected by individuals with extreme readings, are usually given, and from the published data it is not possible to ascertain and compare the blood pressure variations in individuals. In Paper II[1] of this series, an attempt was made to determine if there was any pattern of variability which might be useful in planning a long-term field study of hypertension. Data from a field study, using a standard series of daily blood pressure measurements over a period of 3½ weeks, showed that no single reading or group of readings obtained on a single day was representative of blood pressure variability over the study period. The present paper gives a detailed analysis of the data collected in that field study. Variations in blood pressure under standard conditions are investigated by analysis of the day-to-day and diurnal fluctuations in the same individual, and an attempt is made to determine the number of observations at a single session which will give a satisfactory estimate of the status of an individual's blood pressure.

In Paper I[2] it was pointed out that there are three basic questions on blood pressure measurement which require answer before a satisfactory design of a long-term study can be produced: (a) Under what conditions should blood pressure measurements be made? (b) How many readings at any one time are necessary to obtain a representative picture of the status of a subject's blood pressure at that time? (c) What should be the length of time between observations in a long-term study? The answer to the first question was sought in part by a questionnaire addressed to the Symposium participants.[3] The study reported in Paper II and further analyzed in the present paper was an attempt to get some leads to an answer to the second question. The answer to the third question depends on the answers to the others.

Study supported by funds from the Recess Commission on Hypertension, Commonwealth of Massachusetts.

A summary of the answers to the questionnaire is shown in Table I. These responses do not relate to routine observations, but to observations in a long-term community study of blood pressure. The principal result of the survey is the lack of agreement on the most satisfactory conditions for use in the long-term study design. Opinions were particularly divergent on the number of readings to be taken at the session and on the relative desirability of casual, resting, and basal readings. With respect to basal readings, there were the widest possible differences in definition and methods of measurement. In answer to the question (G. Table I) as to the best method of obtaining basal readings, 5 replied that there was no satisfactory method and 4 that any method is impractical under field conditions; 3 recommended readings during sleep with or without sedation, and 2 immediately on awakening; 2 suggested readings after 10 to 15 minutes rest and 2 preferred rest after no food or drink for 12 to 24 hours; and 1 suggested that readings be made at home by a member of the family. The review of the literature was equally lacking in providing consistent answers to these questions. The most consistent opinion was the necessity for uniformity in the conditions of observations, in the number of readings at each session, and in the observers over the course of the study.

The data presented in this paper are based upon blood pressure readings on 21 subjects observed daily, except Saturday and Sunday, over a period of approximately 3½ weeks. Regular sessions on each subject were scheduled daily at the same time each day, and after an initial casual reading taken in the supine position, subsequent readings were made after 5, 10, 15, 20, and 25 minutes of rest. Fifteen of these subjects were also examined three times daily at 9 A.M., 1:30 P.M., and 4:30 P.M. under the same conditions on one or two occasions. Tables II, IIIA and IIIB give a description of the subjects and a summary of all the observations. These subjects, 10 males and 11 females, representing each decade from 20 to 60, were volunteers chosen without reference to their cardiovascular status from the headquarters staff of the Westchester County Health Department in White Plains, New York.[1] Seven males and 8 females gave no history suggestive of cardiovascular disorders. Two subjects had been told that they had tachycardia and 1 was said to have an arrhythmia without further explanation. One subject had had a coronary occlusion two years before; another, angina fifteen years before; and another had been told he had high blood pressure. In none of these persons was a diastolic pressure of 90 mm. or more sustained during a single session. In 1 subject (No. 13, without cardiovascular history), the systolic pressure was sustained over 140 mm. in 3 of 13 sessions. In 7 subjects, including 4 with suggestive cardiovascular history, diastolic pressures of 90 mm. or above were occasionally recorded either at the initial casual reading or after a period of rest. In 5 subjects, including 3 with histories suggestive of cardiovascular disease, an occasional systolic pressure was recorded of 140 mm. or above. Thus, none of these subjects would be classified as hypertensive, using current criteria. Laboratory studies and physical examinations were not performed. Those with occasional initial diastolic pressures over 90 mm. were compared with the remainder, and no differences were noted in the variability of their blood pressure readings over the study period.

TABLE I. SUMMARY OF RESPONSES TO QUESTIONNAIRE ON BLOOD PRESSURE MEASUREMENT FOR A LONG-TERM STUDY*

A. How many readings should be made at one session so as to establish a satisfactory base to measure change from one examination period to another?

Number of readings†	2	3	4	5	6	3–5	3–15	NO CERTAIN NUMBER
Replies	3	7	2	1	2	2	1	2

B. Should subject be in supine, standing, or sitting position?

Position of subject	SUPINE	STANDING	SEATED	SUPINE OR SEATED	SUPINE AND SEATED	ALL	N.R.‡
Replies	4	0	7	3	1	4	1

C. Is any time of day preferable for taking blood pressure?

Time of day	MORNING	MOST RESTFUL	SEVERAL TIMES	ANY UNIFORM TIME	N.R.‡
Replies	4	1	2	12	1

D. What time should elapse before or after eating?

Relation to eating	UNIMPORTANT	MINIMUM TIME AFTER EATING			NO OPINION	N.R.‡
		½ HR.	2 HR.	3 HR.		
Replies	11	3	2	1	2	1

E. Who should make the blood pressure readings?

Observer	M.D. ONLY	ANY WELL-TRAINED PERSON	M.D. OR R.N.
Replies	8	9	3

F. Should readings be basal, casual, or under some other condition?

Conditions	CASUAL	RESTING	BASAL	C AND R	C, R, AND B	NO PREFERENCE	N.R.‡
Replies	6	3	4	1	2	2	2

G. What is the best method for obtaining basal readings? (See text.)

*Addressed to twenty symposium participants.[3]

†These numbers were suggested along with other suggestions as to position, intervals, and other conditions.

‡No reply.

TABLE II. OBSERVATIONS ACCORDING TO SEX, AGE, CARDIOVASCULAR AND BLOOD PRESSURE STATUS OF TWENTY-ONE SUBJECTS OVER A PERIOD OF THREE AND ONE-HALF WEEKS

AGE	SUBJECT NO.	HISTORY* OF CV DISEASE	TOTAL SESSIONS	NUMBER OF SESSIONS							
				DIASTOLIC READINGS 90 MM. OR OVER				SYSTOLIC READINGS 140 MM. OR OVER			
				TOTAL	SUSTAINED	INITIAL 90+, LATER LOWER	INITIAL <90, LATER ABOVE	TOTAL	SUSTAINED	INITIAL 140+, LATER LOWER	INITIAL <140, LATER ABOVE
A. MALES											
26	6	No	17	0	—	—	—	0	—	—	—
26	11	No	17	0	—	—	—	3	0	1	2
32	8	No	19	1	0		1	0	—	—	—
39	9	High Blood Pr.	19	5	0	2	3	8	0	5	3
42	2	No	16	1	0	0	1	0	—	—	—
49	1	No	17	0	—	—	—	0	—	—	—
52	12	Coronary 2 yrs.	16	4	0	1	3	1	0	1	0
53	7	No	17	0	—	—	—	0	—	—	—
60	3	Arrhythmia	16	0	—	—	—	0	—	—	—
69	13	No	16	1	0	—	1	13	3	8	2
Totals	10	No—7; Yes—3	170	12	0	3	9	25	3	15	7
B. FEMALES											
22	18	No	21	0	—	—	—	0	—	—	—
26	5	No	21	0	—	—	—	0	—	—	—
30	20	No	19	0	—	—	—	0	—	—	—
33	21	Tachycardia	14	1	0	1	0	0	—	—	—
39	19	No	19	0	—	—	—	0	—	—	—
44	16	No	21	0	—	—	—	0	—	—	—
49	14	Tachycardia	20	0	—	—	—	0	—	—	—
51	22	No	19	0	—	—	—	0	—	—	—
59	10	No	18	0	—	—	—	0	—	—	—
59	17	No	20	0	—	—	—	0	—	—	—
61	15	Angina	21	8	0	3	5	2	0	1	1
Totals	11	No—8; Yes—3	213	9	0	4	5	2	0	1	1
Grand Totals	21	No—15; Yes—6	383	21	0	7	14	27	3	15	8

*Subject's replies to specific questions about hypertension and cardiovascular disease.

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Tables IIIA and IIIB give the number of sessions and observations; a summary of the blood pressure readings of every subject*; and the maximum ranges throughout the study period, for individual sessions, and for the diurnal sessions. The range of diastolic pressures encountered over the total period under these standard conditions was between 18 and 24 mm. for 11 subjects; there was one subject with a range below 13 and one above 35 mm. Maximum systolic ranges for about one-half of the subjects were 8 or more mm. larger than diastolic ranges. Although the sample is too small for adequate analysis of age and sex differences, there are no indications that diastolic or systolic pressures, or ranges, vary consistently according to these characteristics.

Six readings were made at each session because this included the recommendations of most of the symposium participants. This was also judged to be the largest practicable amount of time that could be taken under field conditions. One purpose of this study was to determine whether fewer than six readings would be adequate for an estimate of the diastolic and systolic pressure fluctuations. Table IV shows the number of times the lowest and highest pressure was first recorded at the initial reading and at 5-minute intervals of rest in the 383 sessions. The initial diastolic reading at a session was as low as the lowest occurring during that session in 35 per cent of the sessions (second line of table). After 5 minutes of rest, an additional 18 per cent of all sessions had shown their lowest diastolic pressures. After 10 minutes of rest, the occurrence of at least one reading at the lowest level had reached 69 per cent (cumulative per cent line). Comparable percentages are shown in the table of the highest diastolic pressure and for systolic pressure, lowest and highest.

Since differences of 4 mm. or less are usually regarded as nonsignificant differences, tabulations are also included in Table IV of the first occurrence within 4 mm. of the lowest and highest diastolic and systolic pressures. After ten minutes of rest, approximately 90 per cent of the sessions had shown the same extreme readings that were reached in 25 minutes, 93 and 87 per cent for lowest and highest, respectively; and, after 15 minutes, the level had reached about 95 per cent of the maximum variability. It is of interest that the subjects with a positive cardiovascular history reached their lowest pressures just as quickly as the others. Perhaps the most surprising observation in this table is that in two-thirds of the sessions the diastolic pressures on casual examination were not significantly higher than the lowest recorded after as much as 25 minutes of rest in the supine position. Since the initial readings in this study were also taken in the supine position, this observation suggests that much of the transient variability that has previously been reported in examinations on seated subjects may be eliminated in the supine position.

In addition to analyzing the time in the individual sessions which produced the lowest and highest diastolic and systolic readings, an analysis was made of the day in the study period in which the lowest and highest readings first occurred. In Table V it may be seen that the majority of the subjects had reached their lowest *and* highest levels within the first five days. The highest diastolic reading occurred on the first day of observation in 9 subjects, in 14 subjects on

*For considerations of space, the readings are grouped within 4 mm.

TABLE III A. SUMMARY OF DIASTOLIC BLOOD PRESSURE READINGS ON TWENTY-ONE SUBJECTS

	MALE										FEMALE										
Age	26	26	32	39	42	49	52	53	60	69	22	26	30	33	39	44	49	51	59	59	61
Subject number	6	11	8	9	2	1	12	7	3	13	18	5	20	21	19	16	14	22	10	17	15
CV history	No	No	No	Yes	No	No	Yes	No	Yes	No	No	No	No	Yes	No	No	Yes	No	No	No	Yes
No. regular sessions	14	16	17	17	16	15	16	13	12	16	17	17	17	14	17	17	16	17	17	17	17
Hour	1p	4p*	2p*	3p	10a	9a*	9a*	2p	10a*	10a	2p	11a*	3p	3p*	2p*	11a*	10a*	4p	3p*	1p	11a
Diurnal sessions	1	—	1	1	—	1	—	2	2	—	2	2	1	—	1	2	2	1	—	1	2
Total observations	102	102	114	114	96	102	96	102	96	96	126	126	114	84	114	126	120	114	108	120	126
Diastolic readings†																					
97–100																					1
93– 96							1						1								2
89– 92			2	9	2		4			1			2								16
85– 88			8	9	26		10			5			3							1	19
81– 84			7	5	14		31		1	18			6		2		1			0	18
77– 80	5	2	43	25	38		36		38	55			21		12		1			4	46
73– 76	3	2	22	14	14		9	3	15	14			25		19		0	1		8	19
69– 72	19	12	24	27	2		5	15	35	3	4	7	41	2	45	4	5	15	7	39	5
65– 68	17	35	8	19		10		34	7		6	20	10	1	24	6	4	40	26	29	
61– 64	14	6		4		18		19			19	23	3	23	10	38	28	33	14	33	
57– 60	25	29		2		64		30			50	62	2	29	2	64	49	23	51	6	
53– 56	14	8				10		1			21	11		19		12	25	2	10		
49– 52	5	5									26	3		9		2	5				
45– 48		3												1			2				
Maximum ranges‡																					
Total	30	32	27	34	20	12	24	22	14	18	20	20	36	22	22	18	34	19	20	27	28
One session	24	15	20	22	12	10	14	17	12	16	18	17	20	14	14	12	14	10	15	20	18
Diurnal	30	—	22	25	—	10	—	12	10	—	20	12	12	—	14	14	16	10	—	20	22

*Asterisk indicates half hour; e.g., 11:30, 2:30, 9:30, etc.
†At 4 mm. intervals.
‡In mm. Mercury.

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TABLE III B. SUMMARY OF SYSTOLIC BLOOD PRESSURE READINGS ON TWENTY-ONE SUBJECTS

	MALE										FEMALE										
Age	26	26	32	39	42	49	52	53	60	69	22	26	30	33	39	44	49	51	59	59	61
Subject number	6	11	8	9	2	1	12	7	3	13	18	5	20	21	19	16	14	22	10	17	15
CV history	No	No	No	Yes	No	No	Yes	No	Yes	No	No	No	No	Yes	No	No	Yes	No	No	No	Yes
No. regular sessions	14	16	17	17	16	15	16	13	12	16	17	17	17	14	17	17	16	17	17	17	17
Hour	1p	4p*	2p*	3p	10a	9a*	9a*	2p	10a*	10a	2p	11a*	3p	3p*	2p*	11a*	10a*	4p	3p*	1p	11a
Diurnal sessions	1	—	1	1	—	1	—	2	2	—	2	2	1	—	1	2	2	1	—	1	2
Total observations	102	102	114	114	96	102	96	102	96	96	126	126	114	84	114	126	120	114	108	120	126
Systolic readings†																					
149–154										6											
145–148										3											1
141–144		1								14											0
137–140		3	1	9			2			27											3
133–136	1	3	1	6	1		2			13											5
129–132	4	13	2	9	7		14			20			1								26
125–128	2	24	14	23	16		12			6	2		0							1	16
121–124	1	18	15	14	15		25		3	5	1	2	0						2	0	17
117–120	15	23	30	28	29		32	1	13	2	16	15	19		6	1			4	1	37
113–116	9	9	30	10	16		4	3	17		14	10	16		10	0	1	3	1	0	8
109–112	26	8	16	12	9	1	4	8	38		47	61	36	3	45	9	3	9	7	13	10
105–108	25		2	3	3	1	1	15	22		25	24	17	4	22	12	6	21	19	18	1
101–104	13		3			4		16	3		13	12	23	20	25	19	30	28	26	30	2
97–100	6					5		31			7	2	2	33	6	50	57	39	27	35	
93– 96						20		15			1			21		18	22	13	13	16	
89– 92						48		8						3		7	1	1	8	6	
85– 88						23		5											1		
Maximum ranges‡																					
Total	36	32	36	32	29	12	32	32	18	34	30	24	30	18	20	30	22	24	36	38	46
One session	20	24	24	30	25	18	20	13	13	30	16	18	26	10	20	20	18	20	18	32	22
Diurnal	20	—	32	32	—	10	—	27	13	—	24	18	16	—	16	18	16	15	—	16	46

*Asterisk indicates half hour; e.g., 11:30, 2:30, 9:30, etc.
†At 4 mm. intervals.
‡In mm. Mercury.

TABLE IV. FIRST OCCURRENCE OF LOWEST AND HIGHEST DIASTOLIC AND SYSTOLIC BLOOD PRESSURE READINGS AFTER STATED PERIODS OF REST IN 383 SESSIONS WITH 21 SUBJECTS OVER A THREE AND ONE-HALF-WEEK PERIOD

	SESSIONS							SESSIONS						
	FIRST OCCURRENCE OF LOWEST DIASTOLIC AFTER PERIODS OF REST							FIRST OCCURRENCE OF LOWEST SYSTOLIC AFTER PERIODS OF REST						
	INITIAL READING	5 (MIN.)	10 (MIN.)	15 (MIN.)	20 (MIN.)	25 (MIN.)	TOTAL SESSIONS	INITIAL READING	5 (MIN.)	10 (MIN.)	15 (MIN.)	20 (MIN.)	25 (MIN.)	TOTAL SESSIONS
First occurrence—Lowest														
Number of sessions	133	70	60	54	32	34	383	52	91	89	60	51	40	383
Per cent of total sessions	35	18	16	14	8	9	100	14	23	23	16	14	10	100
Cumulative per cent	35	53	69	83	91	100	—	14	37	60	76	90	100	—
First occurrence within 4 mm.														
Number of sessions	256	66	34	11	10	6	383	151	129	61	25	14	3	383
Per cent of total sessions	67	17	9	3	3	1	100	39	33	16	7	4	1	100
Cumulative per cent	67	84	93	96	99	100	—	39	72	88	95	99	100	—
	FIRST OCCURRENCE OF HIGHEST DIASTOLIC AFTER PERIODS OF REST							FIRST OCCURRENCE OF HIGHEST SYSTOLIC AFTER PERIODS OF REST						
	INITIAL READING	5 (MIN.)	10 (MIN.)	15 (MIN.)	20 (MIN.)	25 (MIN.)	TOTAL SESSIONS	INITIAL READING	5 (MIN.)	10 (MIN.)	15 (MIN.)	20 (MIN.)	25 (MIN.)	TOTAL SESSIONS
First occurrence—highest														
Number of sessions	126	59	55	55	33	55	383	196	47	31	41	32	36	383
Per cent of total sessions	33	15	14	14	10	14	100	51	12	8	11	8	10	100
Cumulative per cent	33	48	62	76	86	100	—	51	63	71	82	90	100	—
First occurrence within 4 mm.														
Number of sessions	245	54	33	23	18	10	383	289	41	14	22	7	10	383
Per cent of total sessions	64	14	9	6	4	3	100	75	11	3	6	2	3	100
Cumulative per cent	64	78	87	93	97	100	—	75	86	89	95	97	100	—

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the first two days, and in 19 within the first five days. The latest occurrence of the highest diastolic was the eleventh day. The highest systolic had a wider spread, 13 in the first five days, but in two instances the first occurrence of the highest diastolic was on the last day of observation.

TABLE V. DAY OF FIRST OCCURENCE OF LOWEST AND HIGHEST DIASTOLIC AND SYSYOLIC PRESSURES, WITHIN 4 MM., IN TWENTY-ONE SUBJECTS DURING THREE AND ONE-HALF WEEKS

DAY OF OBSERVATION	DAY OF WEEK	SUBJECTS WITH FIRST OCCURRENCE			
		DIASTOLIC PRESSURE		SYSTOLIC PRESSURE	
		LOWEST* READING	HIGHEST* READING	LOWEST* READING	HIGHEST* READING
1	Thu	3	9	5	7
2	Fri	4	5	4	4
3	Mon	4	2	3	1
4	Tue	2	1	3	1
5	Wed	1	2	—	—
6	Thu	1	—	3	—
7	Fri	—	—	2	—
8	Mon	1	—	—	1
9	Tue	—	—	—	1
10	Wed	1	1	1	—
11	Thu	—	1	—	1
12	Fri	1	—	—	2
13	Mon	1	—	—	—
14	Tue	1	—	—	1
15	Wed	1	—	—	—
16	Thu	—	—	—	—
17	Fri	—	—	—	2
Total Subjects		21	21	21	21

*Within 4 mm. Hg.

With respect to the first occurrence of the lowest pressure readings, the spread for diastolic readings was wider than for systolic. In both diastolic and systolic, the majority reached their lowest level during the second week by the seventh observation day. In three instances the lowest diastolic was not reached until the last week.

Tables VIA and VIB show the mean diastolic and systolic pressures according to age and sex for all subjects and include the highest and lowest means for individual sessions as well as the means of initial readings and of those taken after periods of rest. Column (8) gives the differences between the highest and lowest means of individual sessions. In only 2 subjects (Nos. 1 and 13) were the differences in mean diastolic pressure less than 10 mm.; there were 15 subjects with differences of 10 to 19 mm.; and 4 subjects (Nos. 6, 11, 19, and 20) had differences greater than 20 mm. Examination of the individual protocols reveals that the large differences are not due to one or two unusually high readings in

TABLE VI A. VARIATION OF MEAN DIASTOLIC PRESSURE DURING SEVENTEEN DAYS OF OBSERVATION AND WITHIN SESSIONS AFTER STATED MINUTES OF REST

SUBJECT	AGE	TOTAL OBSERVATIONS		DIASTOLIC PRESSURES									
				MEANS OF ALL READINGS	MEANS OF SINGLE SESSIONS			MEANS OF INITIAL READINGS	MEANS AFTER REST PERIODS				
		SESSIONS	READINGS		LOWEST	HIGHEST	DIFFERENCE (MM.)		5 (MIN.)	10 (MIN.)	15 (MIN.)	20 (MIN.)	25 (MIN.)
COL. (1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)
A. MALE													
6	26	17	102	63.8	54.2	75.8	21.6	66.0	65.5	63.2	63.3	62.6	62.0
11	26	17	102	63.0	51.3	73.7	22.4	62.0	61.9	62.9	63.2	64.1	63.6
8	32	19	114	76.6	67.7	84.5	16.8	75.2	77.1	77.4	76.8	76.6	76.4
9	39	19	114	75.9	60.3	87.7	27.4	78.2	74.9	77.3	74.5	74.3	75.8
2	42	16	96	81.0	75.0	85.3	10.3	79.4	81.7	82.6	81.4	80.2	80.8
1	49	17	102	60.2	56.7	63.7	7.0	58.5	59.2	60.2	60.6	60.9	61.5
12	52	16	96	81.8	75.3	87.3	12.0	80.9	80.4	80.1	0.8	81.7	82.5
7	53	17	102	64.6	58.3	70.3	12.0	65.3	65.5	65.2	64.5	63.4	63.9
3	60	16	96	74.7	69.3	80.0	10.7	74.2	73.8	74.8	75.4	75.3	74.7
13	69	16	96	79.8	73.7	82.7	9.0	81.1	80.1	80.5	78.9	79.6	78.6
B. FEMALE													
18	22	21	126	58.0	51.3	63.2	11.9	59.0	58.0	56.5	56.9	58.7	59.1
5	26	21	126	61.0	54.3	65.5	11.2	61.0	60.0	61.1	60.9	61.5	61.7
20	30	19	114	74.0	65.0	86.0	21.0	74.5	74.1	74.8	73.0	73.9	73.8
21	33	14	84	58.7	53.7	63.7	10.0	60.0	58.7	58.3	58.0	59.0	58.3
19	39	19	114	70.8	63.7	78.3	14.6	70.9	70.4	70.6	70.7	71.1	70.8
16	44	21	126	60.6	55.7	66.0	10.3	59.8	61.1	60.7	60.8	60.1	61.0
14	49	20	120	59.8	58.3	74.3	16.0	58.5	59.4	59.1	59.9	60.0	61.6
22	51	19	114	64.3	58.0	70.5	12.5	63.3	63.5	63.7	64.3	65.1	66.1
10	59	18	108	61.9	57.8	70.0	12.2	61.5	62.3	61.3	62.2	62.2	61.6
17	59	20	120	67.7	61.7	76.5	14.8	68.9	67.7	67.4	66.9	67.6	67.8
15	61	21	126	81.8	74.0	91.3	17.3	81.4	81.9	81.5	82.4	82.0	81.9

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TABLE VI B. VARIATION OF MEAN SYSTOLIC PRESSURE DURING SEVENTEEN DAYS OF OBSERVATION AND WITHIN SESSIONS AFTER STATED MINUTES OF REST

SUBJECT	AGE	TOTAL OBSERVATIONS		SYSTOLIC PRESSURES									
				MEANS OF ALL READINGS	MEANS OF SINGLE SESSIONS			MEANS OF INITIAL READINGS	MEANS AFTER REST PERIODS				
		SESSIONS	READINGS		LOWEST	HIGHEST	DIFFERENCE (MM.)		5 (MIN.)	10 (MIN.)	15 (MIN.)	20 (MIN.)	25 (MIN.)
COL. (1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)
A. MALES													
6	26	17	102	111.3	103.8	130.3	26.5	115.8	111.6	110.4	109.9	110.8	109.1
11	26	17	102	123.1	114.2	133.0	18.8	127.0	120.9	122.4	122.4	123.2	122.6
8	32	19	114	118.0	108.3	125.3	17.0	120.8	116.0	115.6	118.4	118.0	119.4
9	39	19	114	122.9	112.2	133.8	21.6	128.6	121.2	119.6	122.7	121.7	124.0
2	42	16	96	120.0	112.3	128.8	16.5	123.3	119.6	118.8	120.1	118.4	119.7
1	49	17	102	92.1	87.7	102.3	14.6	95.5	91.5	90.9	91.5	91.1	91.8
12	52	16	96	122.9	114.3	131.3	17.0	122.9	120.1	122.6	122.1	124.5	125.3
7	53	17	102	100.5	89.7	112.8	23.1	101.9	100.8	100.6	99.6	99.8	100.6
3	60	16	96	112.0	107.7	119.7	12.0	115.4	112.3	110.4	110.9	111.2	111.6
13	69	16	96	136.4	128.7	147.0	18.3	140.0	135.6	136.0	136.1	134.5	136.3
B. FEMALES													
18	22	21	126	110.4	101.3	118.7	17.4	111.7	109.1	109.7	109.7	110.6	111.3
5	26	21	126	110.7	105.0	115.5	10.5	113.9	111.2	109.5	109.6	110.2	109.9
20	30	19	114	110.6	101.3	118.7	17.4	112.8	111.5	110.2	109.6	109.8	109.9
21	33	14	84	99.7	95.3	107.3	12.0	100.3	100.4	99.6	99.7	99.6	98.6
19	39	19	114	108.5	103.0	118.0	15.0	109.7	107.8	108.4	108.1	108.8	108.4
16	44	21	126	100.9	92.3	109.0	16.7	102.8	101.2	100.7	100.7	100.1	99.9
14	49	20	120	100.2	95.7	104.0	8.3	100.3	100.9	99.7	100.6	9.8	100.0
22	51	19	114	102.3	95.3	109.7	14.4	105.2	102.0	101.0	101.8	102.1	101.7
10	59	18	108	102.5	95.2	120.7	25.5	103.4	103.1	100.9	102.9	102.0	112.4
17	59	20	120	102.1	91.0	108.3	17.3	105.3	101.5	101.3	101.1	101.5	101.7
15	61	21	126	123.1	112.3	135.3	23.0	124.0	122.1	122.0	123.9	124.0	122.5

a session but are characteristic of all readings of the session. Results with systolic pressure comparisons are similar.

Comparison of the mean of all initial readings on a subject during the period of observation with those taken after 5, 10, 15, 20, and 25 minutes of rest are shown in columns (9) to (14) of Table VI. These show that the variation in relation to rest is slight, no subject exhibiting as much as 5 mm. of variation in mean diastolic pressure.

TABLE VII. DIURNAL VARIATION IN MEAN DIASTOLIC PRESSURE

SUBJECT	SERIES	MEAN DIASTOLIC PRESSURES		
		9 A.M. (MM.)	1:30 P.M. (MM.)	4:30 P.M. (MM.)
1	1	59.8	60.8	61.8
3	1	70.8	69.8	73.7
	2	69.3	70.0	70.7
5	1	61.5	61.8	62.3
	2	64.7	62.7	62.2
6	1	57.0	54.7	67.7
7	1	62.7	63.0	68.7
	2	66.2	59.7	65.7
8	1	84.5	70.7	82.0
9	1	82.0	79.8	82.7
14	1	58.0	62.7	60.3
	2	61.3	50.3	54.3
15	1	90.0	74.0	77.3
	2	85.7	77.5	82.0
16	1	60.3	60.7	57.0
	2	60.3	59.7	57.3
17	1	70.7	62.3	76.5
18	1	60.0	61.7	55.7
	2	57.0	53.3	61.3
19	1	70.7	71.0	76.0
20	1	69.3	72.0	72.0
22	1	67.3	65.3	65.0

Contrast between the stability of mean pressures in relation to periods of rest and the wide differences in mean pressures at various sessions is striking and suggests that short periods of rest do not modify materially whatever may be responsible for the day-to-day variation in diastolic pressure.

To obtain information on blood pressure fluctuations during the course of a day, a series of supplementary sessions was conducted on most of these

subjects. Twenty-two series of diurnal observations were made, each series consisting of three 25-minute sessions in a single day at 9 A.M., 1:30 P.M., and 4:30 P.M. The mean diastolic pressures are shown in Table VII. There is no consistent pattern during the day, although there is a tendency (10 instances) for the means in the middle of the day to be slightly lower than the other two. The means of the 4:30 sessions were highest on eleven days, but the difference was greater than 4 mm. on only four days. Subject No. 1 showed a variation of only 2 mm. among the three sessions, while for subject No. 6 the mean diastolic pressure at the three sessions differed by 13 mm. In most instances, the differences were less than 10 mm. Among the 7 subjects who were studied on two days, 3 (Nos. 3, 5, and 16) had similar differences on both days, while 4 subjects (Nos. 7, 14, 15, and 18) did not.

When the diurnal readings are compared with those taken during the regular day-to-day sessions (no table shown), it was found that the highest diurnal diastolic readings were within 4 mm. of the highest routine readings in 6 of 15 instances and within 8 mm. in 12 of the 15 instances. The lowest diastolic diurnal reading was within 4 mm. of the lowest of all the regular readings in 11 instances and within 8 mm. in all instances. There is some indication here that some type of diurnal pattern of blood pressure measurement might serve as an index of blood pressure variation over a longer period. Further study will be required for more definite information on this problem.

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SUMMARY

The results of a questionnaire on conditions of blood pressure measurement, sent out prior to the reported study, revealed wide diversity of opinion as to the most satisfactory conditions for blood pressure measurement.

This is an analysis of individual blood pressure changes over a period of 3½ weeks measured daily at the same hour among 21 subjects observed at 5-minute intervals during a 25-minute period of rest. Fifteen subjects were examined three times on one or more days (9 A.M., 1:30 P.M., and 4:30 P.M.).

Although a few of the subjects in the study had occasional readings above 90 mm. diastolic or 140 mm. systolic, none had sustained pressures above these levels. Among the 383 sessions, the initial casual diastolic reading (within 4 mm.) was the lowest in two-thirds of the sessions. There was little change in readings after 15 minutes of rest.

In comparing the observations extending over 3½ weeks, it was found that the majority of the subjects had reached both their lowest *and* highest levels within the first five days. Although there was some tendency for midday readings to be lower than the other, this pattern was not consistent.

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STUDIES IN HYPERTENSION

IV. Comparison of Reaction to Three Tests for Hyperreactivity Among 204 Volunteers

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MUCH interest has been focused on the clinical observation that blood pressure in patients with hypertension has greater lability than in normal subjects. Hines and Brown[1] introduced the Cold Pressor Test nearly twenty-five years ago as a quantitative measure of blood pressure lability. They showed that the systolic and diastolic pressure were much greater in hypertensive than in normal subjects, and this reaction was designated as *hyperreactivity*. They observed, however, that a small percentage of nonhypertensive subjects also exhibited this hyperreactivity. This led to the hypothesis that the onset of hypertension is preceded by a period in which variability of the blood pressure is exaggerated under stress, while the resting or basal pressure remains within the normal range.

This hypothesis has attracted wide interest because of the hope that it would help elucidate the etiology and pathogenesis of hypertension. During the past decade or so, nearly a score of papers have appeared annually, dealing with this problem. Many aspects of the Cold Pressor reaction have been studied, including the influence of age and sex, and its occurrence in other disorders. In addition, a number of other tests for hyperreactivity have been proposed. There is conflicting evidence on the utility of these tests. The significance of the reaction has been challenged,[2-6] and even when the results obtained by several investigators are in agreement, the interpretations are often contradictory.

The reason for disagreement derives primarily from the fact that no direct evidence has been accumulated to show that hyperreactivity in normal subjects is a precursor of hypertension. Cross-sectional studies executed at one point in time have provided the basis for the inference that this relationship between hyperreactivity and hypertension does exist. However, such studies do not

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furnish proof of the relationship. The need for a longitudinal study of this problem has been expressed on numerous occasions.[7] It has been generally agreed that satisfactory evidence concerning the relation of hyperreactivity in "normal" subjects to the subsequent development of hypertension can best be obtained by observation of a representative sample of the general population over a period of years well in advance of the onset of the disease.[3,8]

In view of these considerations, it is planned to incorporate a study of hyperreactivity in the long-range population study of hypertension which is discussed in the first paper of this series.[9] In order to make this possible, however, it has been considered necessary to review the procedures which have been developed and to test their suitability for use under field conditions. This paper summarizes the results of a pilot study directed to testing the applicability of three tests of hyperreactivity to field use.

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TESTS FOR HYPERREACTIVITY

Although a large number of tests for hyperreactivity have been suggested, a survey of the literature has revealed only three which have been studied on more than a small scale and which might by their nature be considered suitable for field use. These are the *Cold Pressor Test*, introduced by Hines and Brown[10,11]; the *Breath-Holding Test*, developed by Ayman and Goldshine[12,13]; and the *Initial Casual* measurement procedure, the use of which has been proposed by Hines[14] and by Levy, Hillman, Stroud, and White.[15]

Cold Pressor Test.—The significant observation in this test is the elevation in blood pressure which quickly occurs when the hand is immersed in ice-cold water. Hines[10] has recommended that immersion be for sixty seconds in water at 4° C. ± 1° and that the test be performed in the supine position in a quiet room, after the subject has rested, until a stationary low level of systolic and diastolic pressure has been reached. Subjects are considered hyperreactive when the maximum rise in diastolic pressure during immersion is 15 mm. Hg or more, and the systolic rise is 20 mm. Hg or more. Recently, an additional condition has been suggested[3] that the diastolic pressure during immersion should be 90 mm. Hg or higher.

The Cold Pressor Test has been carried out on thousands of subjects and is more widely used than any other suggested procedure. Pain is experienced by most subjects during the test and is sometimes so severe that the test cannot be completed. Several investigators have suggested that the vascular reactivity in a subject is correlated with the amount of pain experienced.[16-18] There is also believed to be an apprehensive or other emotional reaction associated with this test.[18]

Breath-Holding Test.—This test is based on the observation that interruption of breathing for more than a relatively short time will result in a rapid rise in blood pressure. Ayman and Goldshine[12,13] have proposed that after a resting blood pressure has been reached and at the moment of a quiet expiration, the breath be held for twenty seconds. Subjects are considered hyperreactive if the rise in the systolic and/or the diastolic blood pressure is 23 mm. Hg or more.

While this test has not been so widely used as the Cold Pressor reaction, its use has been recommended because of the ease of accomplishment and the

absence of pain, which is an important consideration in field studies with volunteer subjects. A drawback noted is the need for active cooperation by the subject, since even slight inspiration will invalidate the test.

Initial Casual Pressure.—This test is derived from the long-known clinical observation that blood pressure readings taken within the first few minutes of a medical examination will usually give higher readings than measurements taken some minutes later, after the subject is more relaxed and reassured. Levy and his associates[15] have suggested the use of casual readings of at least 150 mm. systolic or 90 mm. diastolic as a criterion of hyperreactivity, provided subsequent readings are below these levels.

Although this is the simplest procedure hitherto suggested, experience with it is still too limited to permit evaluation of its significance.

There are two precautions to be emphasized in the use of these tests for studies of hypertension. First, the pressor mechanisms (one or more) responsible for vascular hyperreactivity in general are unknown. While a variety of neurogenic and humoral pressor mechanisms have been studied, the relation of these to the anatomic and physiologic changes thought to be responsible for hypertension is in dispute. In addition, there is little information available concerning the actual mechanisms of hyperreactivity in specific tests, except for a few studies suggesting the existence of a neurogenic thalamic factor in the Cold Pressor Test. Accordingly, it is hypothetical whether or not the tests are accurate indicators of vascular hyperreactivity.

The second precaution to be considered arises from uncertainty regarding the correlation between hypertension and hyperreactivity as measured by any of these tests. There is agreement that clinical examination of subjects considered hyperreactors and normoreactors, respectively, would reveal a higher proportion of hypertensives in the first group (hyperreactors) and a higher number of subjects in the normal range in the second (normoreactors). However, investigators experienced with these tests[8] hold unanimously to the conclusion that none of the tests and criteria now in use can be used to discriminate, in a single case, a potential hypertensive from a nonhypertensive.

The study reported in this paper is focused on testing the applicability of three tests of hyperreactivity for field use and on examining the amount of agreement obtained in the results of the three tests when administered to the same subjects.

PROCEDURES IN THE FIELD STUDY

The study design required that each of these tests be administered to each subject of a population sample at a single session in the subject's home. Several alternative procedures for doing this were tried on a few volunteer subjects. The procedure finally adopted required the administration of the tests in the following manner.

1. *Initial Casual Blood Pressure Measurement.*—Upon the arrival of the investigator in the subject's home and after a brief introduction, the subject was placed in a supine position and a measure of his blood pressure and pulse rate was taken immediately.

2. *Description of the Procedure to the Subject.*—After taking the initial blood pressure and pulse rate, the investigator described the series of tests to be performed. During this process, the blood pressure cuff was inflated several times to accustom the subject to the experience. The patient was informed about the use of ice water in the Cold Pressor Test and practiced holding his breath for the Breath-Holding Test.

3. *Basal Readings.*—Following the foregoing preliminaries, the patient was encouraged to lie quietly. In the meantime, the investigator took successive blood pressure readings and pulse rates, allowing one-minute intervals between completing one measurement and beginning another. Readings were taken until three successive measurements were obtained in which the difference between the successive systolic and diastolic pressures differed by no more than 8 mm. Hg.

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4. *Breath-Holding Test, Systolic.*—The Ayman-Goldshine Breath-Holding Test was then administered to determine the rise in the systolic pressure.

5. *Return to Basal.*—Same procedure as followed in 3, above.

6. *Breath-Holding Test, Diastolic.*—The Breath-Holding Test was then repeated to determine the rise in diastolic pressure.

7. *Return to Basal.*—As in 3, above.

8. *Cold Pressor Test.*—Blood pressure readings and pulse rates were taken after the subject's hand had been immersed in ice water for sixty seconds, and thereafter at thirty-second intervals for a total of three minutes.*

9. *Return to Basal.*—As in 3, above.

To balance the possible influence on results of the order in which the tests were administered, it was prescribed that the order be reversed on alternate subjects. This required administering the Cold Pressor Test prior to the Breath-Holding Test in half the cases.

The 204 subjects included in the experiment were selected *primarily* from the residents of a housing project in South Boston who were on the rolls of the Home Medical Service of the Boston University School of Medicine and the Massachusetts Memorial Hospitals.†

Within the housing project, 172 families were visited and one or more volunteers were obtained in all but 27 of these families. The balance of the sample was recruited from families outside the housing project, but in the Home Medical Service area. Although no randomizing procedure was used in the recruiting process, an attempt was made to obtain subjects of both sexes and from all age groups. However, the sample finally chosen is more representative of the general

*The method allowed for satisfying the procedural requirements established by Hines, with the exception that the return to basal occurred after the hand had been immersed in ice water for three, rather than one, minutes. However, this modification did not affect the use of the data for the purpose of classifying subjects as hyperreactors or nonhyperreactors according to the Hines criteria. It was done to test the claim that blood pressure continues to rise when immersion occurs for longer than one minute.[19]

†The cooperation of these institutions and particularly of Dr. Henry J. Bakst, Director of the Home Medical Service and Professor of Preventive Medicine, Boston University School of Medicine, is most gratefully acknowledged.

population of the area than if it had been limited to patients in the clinic or volunteers from the hospital. Though all subjects were on the rolls of the Home Medical Service, only a few were under observation or treatment at the time the observations were made.

Although prior appointments had been made in every case, 48 of the original 200 volunteers refused to participate in the experiment when visited by the investigators. Some men, whose cooperation had been volunteered by their wives, were completely surprised by the arrival of the team and refused to be tested. In other cases, potential subjects claimed that they had not understood how much time would be required and refused on the grounds of lack of time. It is likely that fear was the underlying reason for refusal in some of these cases. However, only three persons stated explicitly that their refusal was based on fear of taking the tests. Arrangements were made to obtain substitutes for the refusals from persons residing in the Home Medical Service area and the quota of subjects was thereby fulfilled. The final composition of the sample by age and sex is reported in Table I.

TABLE I. AGE AND SEX DISTRIBUTION OF 186* SUBJECTS ANALYZED FOR HYPERREACTIVITY

AGE	MALE	FEMALE	TOTAL
25 and under	29	35	64
26-40	30	36	66
41 and over	23	33	56
Total	82	104	186

*Only 186 subjects are used in this analysis; 18 were eliminated because of sustained diastolic pressures over 90 mm. None of these patients gave a history of having had high blood pressure.

Testing of the subjects was accomplished during May and June. Seven thoroughly instructed investigation teams, each composed of one fourth-year student at the Boston University School of Medicine and one student nurse, administered the tests, each team testing an average of 28 subjects.

ANALYSIS OF THE RESULTS

An immediate and striking result of the field study was that no subject elected to discontinue his participation once the actual testing was under way. It can reasonably be concluded that when appropriately introduced and properly administered, a measure of the Initial Casual blood pressure and the Cold Pressor and Breath-Holding tests are suitable, without modification, for use under field conditions.

The proportion of the sample identified as hyperreactive by each of the three tests is shown in Table II. The criteria of hyperreactivity used were those of the tests' originators, as reported earlier in the description of the three tests.

Of the study group, 14.5 per cent were identified as hyperreactive by the criteria of the Initial Casual pressure test; 30.1 per cent by those of the Cold Pressor Test; and 25.3 per cent by those of the Breath-Holding Test.

TABLE II. REACTIONS AMONG 186 SUBJECTS TO EACH OF THREE TESTS FOR HYPERREACTIVITY

TEST	NUMBER OF SUBJECTS	NOT HYPERREACTIVE		FULFILLED CRITERIA FOR HYPERREACTIVITY	
		NO.	PER CENT	NO.	PER CENT
Initial Casual reading	186	159	85.5	27	14.5
Cold Pressor	186	130	69.9	56	30.1
Breath-Holding	186	139	74.7	47	25.3

To determine the extent to which subjects classified as hyperreactors to one test are also classified as hyperreactors to another, the results of the several tests were compared. Table III compares the reaction of the subjects to pairs of tests—to the Cold Pressor and Initial Casual Pressure tests, to the Cold Pressor and Breath-Holding tests, and to the Breath-Holding and the Initial Casual Pressure tests.

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TABLE III. REACTION OF 186 SUBJECTS TO COMBINATIONS OF TWO TESTS FOR HYPERREACTIVITY

REACTION TO TESTS	TEST COMBINATIONS					
	COLD PRESSOR AND INITIAL CASUAL		COLD PRESSOR AND BREATH-HOLDING		BREATH-HOLDING AND INITIAL CASUAL PRESSURE	
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
Concordant on both tests—Total	125	67.2	117	62.9	132	71.0
Hyperreaction to both	11		17		10	
Hyperreaction to neither	114		100		122	
Discordant on both tests—Total	61	32.8	69	37.1	54	29.0
Hyperreaction only to Cold Pressor	45		39		—	
Hyperreaction only to Initial Casual	16		—		17	
Hyperreaction only to Breath-Holding	—		30		37	
Grand total	186	100.0	186	100.0	186	100.0

Table III shows that whatever two tests are compared, a significant proportion of the subjects are classified as hyperreactors by one test and not by the other. The greatest concordance is achieved between the Breath-Holding and the Initial Pressure tests, where 71.0 per cent of the subjects were classified in the same ways by both tests. The corresponding figure for the Cold Pressor-Initial Pressure combination was 67.2 per cent, and 62.9 per cent for the Cold Pressor-Breath-Holding combination. It is to be noted, however, that of the

186 subjects, only 10 to 17 of them were identified as hyperreactors by any combination of two tests. A considerably greater number of subjects were classified as hyperreactors by one test and not by the others.

It is obvious that when the results of the *three* tests are compared coincidently, the concordance will be even less than when only two tests are compared. Here, concordance is achieved only where all three tests classify the subject in the same way—either as a hyperreactor or not. The results of a three-way comparison are reported in Table IV.

TABLE IV. REACTION OF 186 SUBJECTS TO A COMBINATION OF THREE TESTS FOR HYPERREACTIVITY

REACTION TO TESTS	NUMBER	PER CENT
Hyperreaction to all	5	2.7
Hyperreaction to none	89	47.8
Concordant on three tests	94	50.5
Hyperreaction to Cold Pressor only	33	17.8
Hyperreaction to Breath-Holding only	25	13.5
Hyperreaction to Initial Casual only	11	5.9
Hyperreaction to Cold Pressor and Initial Casual only	6	3.2
Hyperreaction to Cold Pressor and Breath-Holding only	12	6.4
Hyperreaction to Breath-Holding and Initial Casual only	5	2.7
Discordant on three tests	92	49.5
Grand total	186	100.0

The figures reported in Table IV show that the three tests produce equivalent classifications for 50.5 per cent of the subjects. However, the size of this figure is primarily accounted for by the fact that 89 of the 186 subjects were classified as normoreactive by all three tests; 5 subjects were classified as hyperreactive by all three tests; 23 by two of the three tests; and 69 by only one of the three tests.

The relative lack of concordance may in part be due to the differences used in the three tests to identify hyperreactivity. It may also result from differences in the stimulus which the different tests introduce, and it is possible that subjects differ in the way their vascular systems respond to each stimulus. On those subjects on whom the results are concordant, it can be inferred that the vascular system responded to the stimulus introduced by each test in a similar way. Further work is necessary to discover the conditions under which concordant and discordant results are achieved.

SUMMARY AND CONCLUSIONS

Vascular hyperreactivity is considered by some to be a forerunner of essential hypertension, but at present the evidence is not conclusive. In order to determine how this hypothesis might be tested in a projected long-term study, a pilot field study was was undertaken among 204 persons living in the area served by the Home Medical Service of the Boston University School of Medicine. In a single session in the subjects' homes, three tests of hyperreactivity

were performed to determine the feasibility of doing such tests under field conditions and to examine the concordance of the results for the classification of persons as hyperreactors and nonhyperreactors.

The results serve the positive purpose of showing in a conclusive way that the Cold Pressor Test, the Breath-Holding Test, and the adaptation of the Initial Casual Pressure as a measure of hyperreactivity can be effectively administered under field conditions in subjects' homes. While some subjects were hesitant about taking the tests, those who agreed to do so completed the entire series of tests. This is all the more remarkable when it is considered that the modification of the Cold Pressor Test used in the field study requires that the subject keep his hand in ice water for a total of three minutes.

Concerning one more important matter of testing the concordance of the results obtained from three hyperreactivity tests, the field study showed that no one test could be used in preference to another or as a substitute for the others. From the viewpoint of a long-term epidemiologic study of hypertension, it is clear that the experiment does not provide a basis for deciding which test of hyperreactivity should be incorporated in its design. Presumably, if such a study were to be done immediately, it would be reasonable to include as one of the periodic observations the series of tests used in this field study. However, this would involve some measure of faith that the inadequacies of the tests as noted above could be resolved in the course of such a study. Before this is done, it would seem more desirable to continue further experimentation to test the concordance and, in addition, the reproducibility of the several tests when repeated on the same sample over a short period of time. This would allow some conclusions to be drawn as to the conditions under which concordance is achieved and also indicate whether the tests in combination or alone provide a means for clarifying the phenomenon of hyperreactivity.

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KYPHOSCOLIOSIS AND HEART DISEASE

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CLINICAL and autopsy reports of kyphoscoliosis with its respiratory and circulatory consequences have appeared in the medical literature for at least one hundred fifty years, with recent emphasis on the pathologic physiology of the disorder. Although considerable uniformity of thought has been expressed about many of the clinical features, certain remarkable differences have been evident, particularly in concepts of the underlying mechanisms. The anatomic and functional features of kyphoscoliosis are so variable that a uniform clinical and physiologic picture could hardly be expected. Some of the disagreement concerning pathologic physiology has probably been the result of vagueness about the ventilatory and circulatory readjustments that occur generally in chronic cardiopulmonary diseases. During the last two decades many of these phenomena have been clarified by the work of Cournand and his associates,[1] and a unified picture of the physiologic changes of kyphoscoliosis appears now to be possible.

In 1939, Chapman, Dill, and Graybiel, in a critical review,[2] sifted all the clearly established observations from the morass of speculation and were able to present a clear and precise picture of this disease group. Two outstanding features emerged. First, life expectancy was short, the average age at death of 79 patients being 30 years. Second, heart failure, when it occurred, resembled no other type of heart disease. Chapman and his associates[2] referred to it as pulmonocardiac failure and stated, "This syndrome of pulmonocardiac failure is not analogous to the usual cor pulmonale or to Ayerza's disease. It stands alone in its peculiar manifestations."

During the past seven years, 22 cases of kyphoscoliosis with heart disease have been observed in the Yale Cardiopulmonary Laboratory. Although these cases are anatomically similar to those of Chapman and associates, the natural history in our patients has been so much at variance with their description that a re-evaluation seems in order. Particularly striking is the relatively long life span of the present group, and the clear-cut cor pulmonale pattern found in many of the patients. Evidence that chronic infection, partially controlled during the twenty-year period of sulfonamides and antibiotics, has an important influence on the course may be a clue to the changed character of the disease. For the most part, the cases of Chapman and associates were observed before the antibiotic drug era.

MATERIAL

All patients from the inpatient and outpatient services of the Grace-New Haven Community Hospital who were referred to the Cardiopulmonary service (because of cardiorespiratory symptoms) during the past seven years were included in this study if they showed both kyphosis and scoliosis of sufficient severity to merit the clinical and radiologic use of the terms. We have no data as to the frequency of asymptomatic kyphoscoliosis in the population as a whole, nor can we estimate the probable proportion of such persons who will develop cardiorespiratory symptoms.

OBSERVATIONS

Of the 22 patients, 4 have been lost to follow-up, 3 have died, and 15 are still under observation.

The 22 patients are evenly divided as to sex, 11 male and 11 female. The male:female sex ratio is 7:3 for all the patients referred to the Cardiopulmonary service for all types of cardiopulmonary disease. Only 3 of the present group are Negro, 19 white. The causes of the deformity and their frequency are listed in Table I. Definite or probable Pott's disease headed the list, the next largest category being of "unknown cause." Poliomyelitis and severe trauma followed, with congenital malformations accounting for 2 and pleural and parenchymal lung fibrosis for 1 case each.

TABLE I. FREQUENCY OF THE CAUSES OF KYPHOSCOLIOSIS IN 22 PATIENTS

CAUSE	NUMBER
Probable Pott's disease	5 } 8
Pott's disease	3 }
Unknown	4
Poliomyelitis	3
Trauma	3
Congenital	2
Pleural disease (fibrosis)	1
Fibrosis of one lung	1
Total	22

The deformity occurred in infancy or childhood in 18 patients, and over the age of 20 in 4. The average age of all patients on first visit was 48 years, the median 49, and the range 19 to 78. Of the 3 who died, the average age at time of death was 36 (19, 34, and 55). In the 12 patients showing evidence of congestive heart failure, the average duration of severe dyspnea or other symptoms was seventy months. Intractable heart failure was not the cause of death in the 3 patients who died.

Important complications were heart failure, infection, or embolic phenomena. Of the 22 patients, 7 had had at least one episode of pneumonia and these 7 had a total of 16 pneumonic episodes. Four had had severe influenza in the 1918 epidemic. Three had proved bronchiectasis although 2 of these had no history suggesting previous pneumonia. All of the 22 patients had had bronchitis, bronchiectasis, or pneumonia.

Other complications found were: hyperthyroidism 1, myxedema 1, renal calculus 1, hiatus hernia with gastrointestinal bleeding 1, papillary cystadenoma of the ovary 1, portal cirrhosis 2, and arrested physical development of undetermined cause 1. One patient had a positive serologic test for syphilis which had not reverted on treatment. Recurrent episodes of asthma without obvious infection occurred in 4 patients.

Emotional problems severe enough to warrant psychiatric consultation were present in 5 of the 22 patients. In each of them the difficulty seemed to be related to the effect of physical appearance or disability on interpersonal relations.

Autopsies were performed on the 3 patients who died. Two had pathologic evidence of multiple systemic thrombotic phenomena with pulmonary embolism and infarction, and one had widespread bronchopneumonia. In each, the right ventricle was dilated, its wall hypertrophied, and there was hypertrophy of the left ventricle as well. There was chronic passive congestion of the viscera in all three. In spite of varied heart murmurs heard during life, all valves were normal. In each case the pathologist commented on the distorted shape of the lungs, with areas of compression alternating with extensive areas of emphysema and fibrosis. An unexpected finding in one of the patients was a moderately advanced portal cirrhosis of the liver.

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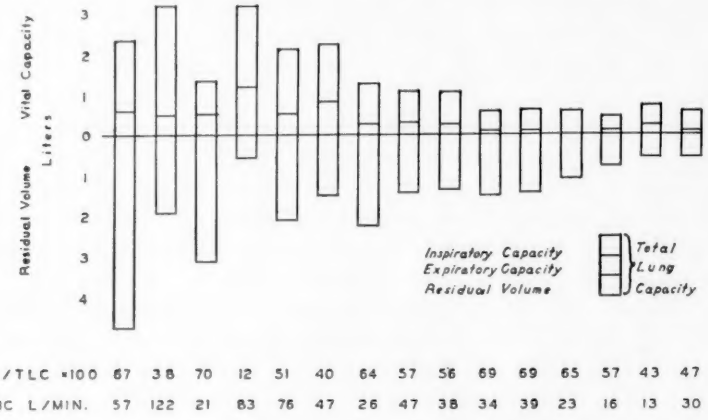
All but one of the 22 patients complained of dyspnea of varying severity. The single exception had other evidence of mild congestive failure (ankle edema, tachycardia), and the absence of dyspnea was attributed to an uncommonly indolent existence. Definite evidence of congestive heart failure was present in 12, 10 of whom responded to digitalization. Thirteen patients complained of chronic cough which was productive of purulent sputum in 7.

The convexity of the scoliosis was to the right in 15 patients. Cyanosis or clubbing was present in 7 patients but occurred together in only 5, 2 patients having only one or the other. Systemic hypertension with a diastolic blood pressure above 100 mm. Hg was found in 7 patients, and an additional 7 patients had diastolic pressures consistently between 90 and 100 mm. Hg. A resting pulse rate of over 100 per minute was found in 14 of the patients.

Laboratory studies revealed a hemoglobin concentration above 15 Gm. per cent in 6 of the 22. Of 13 patients on whom blood serum electrolytes were measured, sodium was below 129 meq. per liter in 1, chloride below 95 meq. per liter in 6, and carbon dioxide above 29 meq. per liter in 7. Five of 15 patients had serum globulin fractions above 5 Gm. per cent. Bacterial cultures were made of the nose and throat and sputum in 7. *Staphylococcus aureus* and *Pneumococcus* were found in 3 each; *Staphylococcus albus*, gram-positive diplococci, and *Hemophilus influenzae* in 2 each; *E. coli*, *Streptococcus viridans*, diphtheroids, and *Neisseria catarrhalis* in 1 each. Skin tests for tuberculosis were positive in 8 of 9 patients. Direct examination and cultures of the sputum for acid-fast bacilli were done in all patients, and none was found.

An electrocardiogram was obtained in 19 patients. It was normal in 5, revealed left axis shift in 7, right axis shift in 6 (with right ventricular hypertrophy in 2), and atrial fibrillation in 1.

Chest roentgenograms were obtained in all cases. These studies were helpful in analyzing the bony deformity, but in only 6 could the radiologist describe an enlarged heart. In the remainder, the distortion was too great to permit a cardiac diagnosis. Two incidental findings were a massive hiatus hernia in one and an aneurysm of the left pulmonary artery in another.



RV/TLC ×100	67	38	70	12	51	40	64	57	56	69	69	65	57	43	47
MBC L/MIN.	57	122	21	83	76	47	26	47	38	34	39	23	16	13	30

Fig. 1.—Lung volumes, ratio of residual volume to total lung capacity (RV/TLC), and maximal breathing capacity (MBC) in 15 patients with kyphoscoliosis.

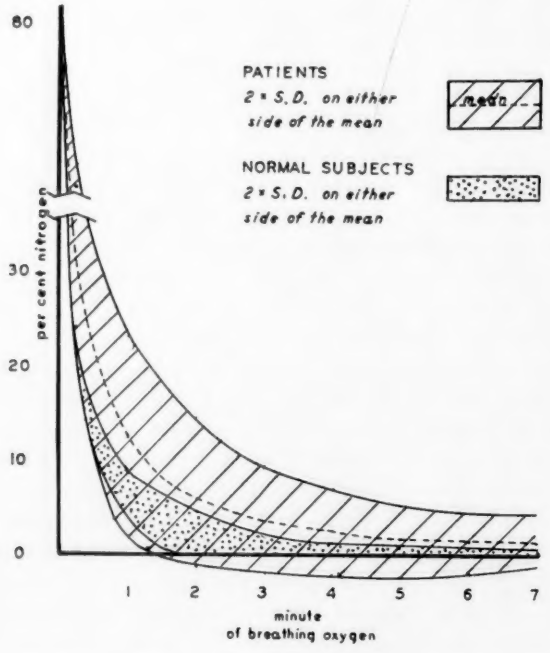


Fig. 2.—The concentration of end-tidal nitrogen during oxygen breathing, a measure of intrapulmonary mixing of respiratory gas, in patients with kyphoscoliosis.

The pulmonary function studies in 15 cases (Fig. 1) revealed the expected total decrease in lung volume in all but 3. The ratio of residual volume to total lung capacity was above normal (25 per cent) in 14 and above 50 per cent in 10. The low vital capacity in most cases is consistent with other reported observations[2]; the low maximal breathing capacity could be anticipated from the thoracic deformity plus the high incidence of congestive heart failure at the time of study. Mean end-tidal nitrogen concentration during oxygen breathing was estimated in 9 cases and found to be above normal in 4. The range, as indicated by standard deviation was greater than normal (Fig. 2). Arterial blood-oxygen saturation studies were done by direct arterial puncture or oximetry in 16 patients and saturation was found to be below normal in 7. However, in only 4 of 14 patients in whom it was again estimated after oxygen breathing did the saturation fail to reach 100 per cent (Fig. 3).

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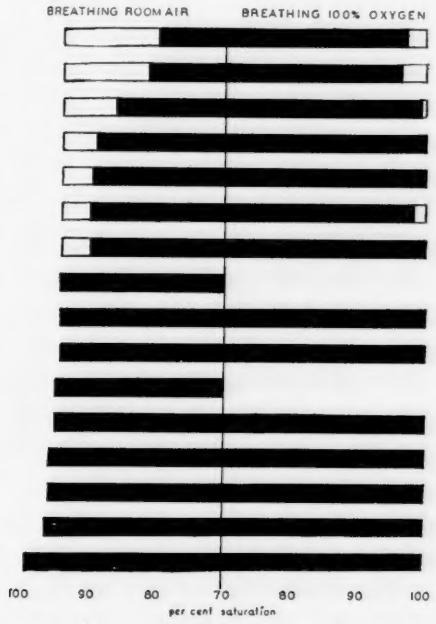

Fig. 3.—Arterial oxygen saturations before and after breathing pure oxygen in 16 patients with kyphoscoliosis. The solid bars represent observed values, open bars represent a deficit from normal. In 2 patients, no observations were made after breathing oxygen.

Cardiac catheterization was done in 4 cases (Table II). The arterial oxygen saturations were lowest and the pulmonary artery systolic pressures highest in the 2 oldest patients. In all 4 cases, right heart pressures were elevated, although the first 2 patients were not classified clinically as having evidence of congestive heart failure.

TABLE II. DATA OBTAINED BY CARDIAC CATHETERIZATION IN 4 PATIENTS

PATIENT	SEX	AGE	ARTERIAL OXYGEN SATURATION %	PRESSURE, MM. HG				SYSTEMIC BLOOD FLOW LITERS/ MINUTE
				F.A.	P.A.	R.V.	R.A. (MEAN)*	
1	M	30	90	130/80	36/25	35/15	12	5.11
2	F	34	94	120/70	35/20	34/10	10	2.94
3	F	41	81	124/70	45/25	45/15	15	4.57
4	F	47	80	118/76	48/26	47/8	10	3.10

*F.A. = femoral artery; P.A. = pulmonary artery; R.V. = right ventricle; R.A. = right atrium.

DISCUSSION

The clinical picture of kyphoscoliosis appearing from these data is one of long-standing thoracic deformity, frequently complicated by pulmonary infection or asthma, increasing exertional dyspnea, and, finally, congestive heart failure which is sometimes but not always of a pure, right-sided type. Neither the cause of the deformity nor the age at which the deformity begins appears to alter the course. As failure supervenes, cardiopulmonary dysfunction is manifest by clubbing, cyanosis, anoxia, secondary polycythemia, and carbon dioxide retention. Pulmonary function studies, although indicating remarkably small total lung volume, are generally of the type seen in chronic fibrosis and emphysema with a particularly impressive increase in the residual volume to total lung capacity ratio. The poor index of intrapulmonary mixing of respiratory gases (nitrogen clearance) and low arterial blood oxygen saturation are similar to observations in patients with other types of fibrosis and emphysema.

Although the lung is a very compliant and elastic-like structure, prolonged serious change in its shape must lead to one or both of two structural changes, compression or distention. In the deformed chest of the kyphoscoliotic both changes must occur early. Reports in the literature support this as do the 3 autopsy cases of the present series. The compressed lung segments become areas in which bronchial defense mechanisms are impaired and chronic infection becomes inevitable. The consequences of chronic infection are focal fibrosis (with further compensatory distention of adjacent lung as the fibrotic areas shrink) and chronic bronchitis with its consequent cough, bronchial obstruction, and peribronchial fibrosis, all of which lead to more distention. Thus there are three forces leading to overdistention: (1) abnormal shape; (2) shrinkage

of fibrotic areas; and (3) progressive bronchial disease. The result of long-standing pulmonary distention is emphysema with its associated hypoxia, hypercapnea, polycythemia, and increased pulmonary vascular resistance, all leading to pulmonary hypertension.

In those patients in whom cardiac catheterization was accomplished, increasing pulmonary hypertension with right-sided heart failure appeared to be related to age. In contrast to the cases of Chapman and associates[2] in which arterial hypoxia was seen in only 1 of 8 patients and clubbing not at all, the present series revealed hypoxia in 7 of 16 patients and clubbing in 6 of 22. Approximately one-third showed right ventricular patterns on the electrocardiogram. This is about the average for chronic pulmonary disease with heart failure in this clinic. The high incidence of systemic hypertension observed in the present group of cases has been reported in other types of emphysema.[3] The carbon dioxide retention and low serum chloride concentration occurring together in 5 cases is part of the pattern seen in chronic pulmonary insufficiency with cor pulmonale, and in 2 cases it corrected itself with intensive inhalation therapy.[4] In one severely incapacitated patient no carbon dioxide retention was found.

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Nothing except the common denominator of thoracic deformity distinguishes the cardiopulmonary features of kyphoscoliosis from numerous other types of chronic lung disease which culminate in ventilatory insufficiency and cor pulmonale. The paucity of clear-cut signs of right heart failure found in some of these patients has also been observed in other types of chronic pulmonary disease,[5,6] as has the high incidence of systemic hypertension[3] which may obscure the evidence of right-sided failure.

When these data observed in kyphoscoliotic patients are compared with those found in other types of emphysematous subjects, little difference is found. The conclusion that kyphoscoliotic heart disease may be a variant of chronic emphysema and cor pulmonale becomes apparent. This is consistent with the conclusions of Lewis and associates.[7] Kinking of the great vessels as a possible cause of heart failure has been suggested,[8,9] but seems unlikely to be an important factor. Unquestionably, the early appearance of dyspnea is largely a matter of poor ventilatory mechanics. The ultimate cardiopulmonary pattern requires years for its development.

The age data are of particular interest. Earlier reports have emphasized a short life expectancy (only thirty years in 79 of the cases reviewed by Chapman and his associates[2]). They found that the life span after the onset of severe cardiac failure or dyspnea was only five months in 18 of their cases. In a smaller series, Kerwin[10] found a somewhat better outlook for longevity. Two factors which might well explain the better prognosis found in the present series of cases are the improved control of respiratory infections with the advent of antimicrobial agents, and more efficient methods of managing heart failure. Even one or two decades ago, infection and heart failure constituted overwhelming threats to these patients. Today, these threats are less pressing. The high incidence of pulmonary infection in the kyphoscoliotic patient has been noted before (Bachman, quoted by Chapman[2]), and this is probably an important contributing factor to the progressive character of the pulmonary insufficiency. Infection

may, in fact, be the terminal event. However, the use of antibiotics in recent years has prevented many of the lung-destroying types of infection and may gradually eliminate infection as a serious factor.

The number of patients in this series in whom an elevated serum globulin fraction was found (5 of 15) is noteworthy. Although electrophoresis was done in only one case, a high gamma peak with a broad base was demonstrated in that case. Of the 5 patients with hyperglobulinemia, 2 had each had 2 episodes of pneumonia; one had had 1 episode of pneumonia plus repeated hemolytic streptococcus tonsillitis; one had had influenza; and one had never been known to have acute respiratory infection. The latter patient developed myxedema and thyroid swelling of unknown type while under observation. Furthermore, she had had a presumed false positive serologic test for syphilis. All 5 patients had long-standing chronic bronchitis with copious quantities of purulent sputum. Multiple myeloma, sarcoidosis, and lymphogranuloma venereum were considered in each, but no positive evidence for these diseases could be found. Chronic infection per se seems the most likely cause of the hyperglobulinemia in these cases. None of the patients had low globulin fractions.

The higher incidence of hypoxia and finger clubbing in this series of patients with thoracic deformity compared to Chapman's series (in which there was no clubbing) may be due to the greater longevity with a correspondingly better chance to develop chronic respiratory insufficiency.

Of the 12 patients in whom evidence of congestive heart failure was found, 3 were lost to follow-up, 3 died, and the remainder have been maintained in reasonable comfort for two to eight years on the usual cardiac regimen of digitalis, mercurial diuretics, and ammonium chloride. Phlebotomy was performed in patients whose hematocrit was over 50 per cent. Other aids in management have included Diamox and aminophylline. One patient rapidly accumulated edema and pleural effusion when inspiratory positive pressure breathing treatment was started. The edema cleared after cessation of the treatment. The reason for this response is not clear, but other studies have shown that inspiratory positive pressure breathing may transiently increase pulmonary distention, leading to poor intrapulmonary mixing of respiratory gases.[11] Three other patients who presented with severe symptoms showed improvement on inspiratory positive pressure breathing. Four patients demonstrated poor tolerance for high concentrations of oxygen during critical periods of failure or infection, developing somnolence, depressed respirations, and rising serum carbon dioxide levels. These patients did much better on intermittent oxygen plus aerosol therapy, inspiratory positive pressure breathing, and postural drainage. Both ventilatory insufficiency and heart failure in kyphoscoliotic patients should be treated vigorously but with caution. When this is done, the outlook appears to be much less dismal than previously thought. Many of these patients had had multiple hospital admissions at times when they appeared *in extremis*. The use of antibiotics and drugs to improve circulatory and ventilatory function (including inhalation therapy) seemed to reverse a rapidly deteriorating condition, following which there was a period of weeks or months of relative well-being. Thus, vigorous support during acute crises is as important as continued treatment of the ventilatory insufficiency and the treatment of infection when it is present.

Some of the characteristics of kyphoscoliosis described in earlier reports[2,7,12] have not been found in this study. For instance, the previously reported preponderance of males was not found, the sex ratio in the present series being 1:1. The heart failure in this group does not, as in the group reported by Chapman and his associates, appear to "stand alone," but, rather, falls into the heterogeneous group of patients suffering from chronic lung disease with cor pulmonale.

The dramatic consequences of the deformed chest, striking for their social and emotional as well as for their physiologic effects, constitute a warning to the physician managing patients with diseases etiologically associated with kyphoscoliosis[13] and to the thoracic and cardiovascular surgeons whose most gratifying immediate results may subsequently be thwarted by the development of cardiopulmonary insufficiency. The deformity of Pott's disease and poliomyelitis should be preventable as should the deformities subsequent to surgery of the thoracic cage itself, or of the underlying structures.

In recent decades, some advance may have been made in prolonging the life and increasing the functional capacities of the kyphoscoliotic. Nevertheless, the inexorable progress of events leads to ultimate failure of the respiratory and circulatory systems. These consequences can be avoided only by preventing the kyphoscoliosis itself.

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SUMMARY

1. Clinical and physiologic data in 22 cases of kyphoscoliosis are presented.

2. The natural history of the disease as observed in this series was similar to that of chronic pulmonary emphysema with cor pulmonale.

3. Long-standing chronic pulmonary infection played an important role in the course of the disease.

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THE INCIDENCE OF MULTIPLE MYELOMA

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STATISTICAL studies of multiple myeloma are few. The disease is not common, and the number of patients treated by any individual or institution is relatively small. Series of 98, 83, 75, and 61 cases have been reported by Snapper, Turner, and Moscovitz,[1] Bayrd and Heck,[2] Schwartz and Cataldo,[3] and Brownell,[4] respectively. Apart from the question of sample size, such material is unsuitable for calculation of incidence since the size of the related population is unknown. A number of organizations publish statistical material on deaths from multiple myeloma in defined populations,[5,6] but these have been utilized in epidemiologic studies only to a small extent.[7] In addition, there are many possible errors in the clinical diagnosis of this condition, and information as to the accuracy of diagnoses from death certificates and similar sources is lacking.

In a previous report,[8] we have described an investigation in which an attempt was made to obtain clinical and pathologic records of all residents of Brooklyn* diagnosed as having leukemia in the period 1943 to 1952. Concurrently with that study, similar data on other lymphomatous diseases were assembled so that epidemiologic patterns of the different pathologic entities could be compared in the same population. In the present report, the data on multiple myeloma are presented. Estimates of incidence obtained from this material are compared with statistical material on deaths from this disease in the United States and other countries obtained from the World Health Organization's Epidemiologic and Vital Statistics Report.[6]

BROOKLYN MATERIAL

The sources of data are the same as those described in the leukemia study referred to above.[8] Briefly, the records of 34 Brooklyn hospitals (comprising 95 per cent of the general and chronic, other than mental, disease hospital beds in the borough) and a number of selected hospitals elsewhere in New York City were surveyed for all cases of multiple myeloma occurring in residents of Brooklyn and diagnosed for the first time in the period 1943 to 1952. The diagnosis was accepted upon confirmation of the clinical diagnosis by either (a) pathologic

*One of the five boroughs of New York City.

diagnosis made on autopsy (53 cases), marrow biopsy (147 cases) or other biopsy (22 cases); or (b) radiologic diagnosis supported by either serum hyperglobulinemia (11 cases) or Bence Jones proterinuria (5 cases). Cases diagnosed on radiologic evidence alone were not included. Two hundred and eighty-eight abstracts, containing information on 238 patients, were obtained in the hospital survey. (An "abstract" here covers the experience of an individual patient with one institution regardless of the number of separate admissions to that institution. Thirty-eight patients had been admitted to two hospitals and six to three.)

During the same period (1943 to 1952) there were 267 Brooklyn residents who died in one of the five boroughs of New York City whose death certificates indicated multiple myeloma as the primary or contributory cause of death. Hospital information was found for 201 of these, of which 182 were included in the series. Seven were first diagnosed prior to 1943 and in 12 the diagnosis could not be confirmed. Among the 66 death certificates for which corresponding hospital information was not found were 41 in which the item "duration of illness prior to death" indicated a probable onset in the period 1943 to 1952. These 41 patients were included in the series; the other 25 were not. Death certificates not bearing the diagnosis of multiple myeloma were found for an additional thirteen patients known from hospital records to have died from the disease in New York City in the period.

The final series therefore consists of 279 patients. Hospital and death certificate information are available for 195, hospital information alone for 43, and for 41 the diagnosis rests on death certificate information only.

The total number of patients found by this combined hospital and death certificate survey (279) is only slightly higher than that which would have been included in a study of death certificates alone (267). At least in this area, death certificates give a satisfactory picture of the number of patients with multiple myeloma who reach the stage of hospital diagnosis. The death certificate bore the diagnosis of multiple myeloma in all but 13 of the 200 Brooklyn patients known from hospital records to have died in New York City during the period. The diagnosis was confirmed in all but 12 of the 214 deaths for which hospital records were found and was proved incorrect in only 5. These findings have, of course, a strictly local applicability.

INCIDENCE IN BROOKLYN

The mean incidence of multiple myeloma in the white population of Brooklyn during the period of the survey was 10.0 new cases per million population per annum. There was considerable increase in the number of newly diagnosed cases from year to year. During the last four years (1949 to 1952) the mean annual incidence was 14.1 per million. It is necessary to recognize, of course, that even this last estimate is a minimal one, for, although multiple myeloma has been recognized for many years, the wide application of several important diagnostic tests is of very recent development. Even by this minimal estimate, however, using the age and sex-specific risks shown later in this article, the cumulative risks of developing multiple myeloma by the age of 70 are about

1.4 and 1.2 per thousand white males and females, respectively. It is apparent that multiple myeloma is by no means the rarity that it was considered to be twenty years ago.

DEATH RATE IN THE UNITED STATES

Statistical data on deaths from multiple myeloma in the United States as a whole are available for years corresponding to the later years of this survey. Annual death rates in whites in the United States were 7.7, 8.6, 9.4, and 10.1 for the individual years 1949 through 1952; the mean for the four years was 8.9 deaths per million. The higher rate found in Brooklyn for the same years (14.1 per million) probably reflects in part the increasing secular trend in the disease (since incidence rates determine death rates a few years in advance) as well as greater opportunities for diagnosis in a metropolitan area. If this is so, continued increase in the death rate for the country as a whole may be anticipated.

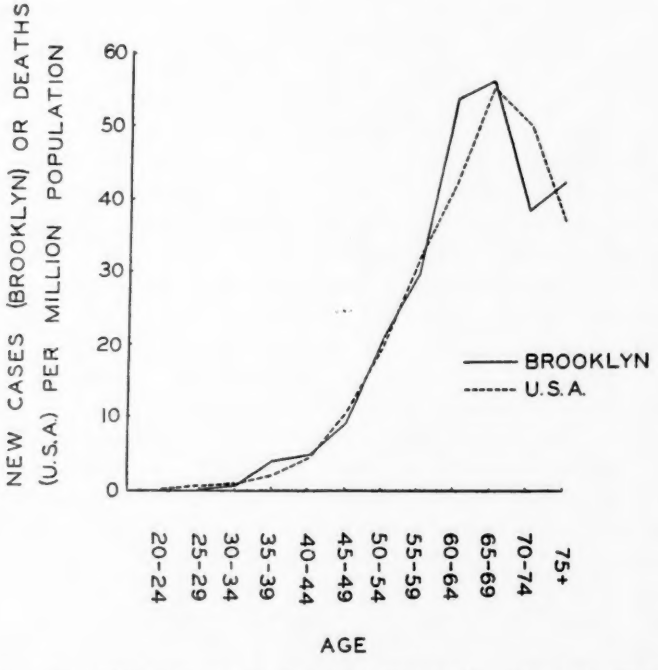

Fig. 1.—Incidence of multiple myeloma related to age at diagnosis (Brooklyn, 1943-1952) and to age at death (U. S. A., 1951-1952)

SEX INCIDENCE

In the Brooklyn data, separate sex incidences were 10.8 for males and 9.2 for females, the corrected sex ratio being 54.0 per cent male. For United States deaths the proportion was similar—55.4 per cent.

Geschickter and Copeland,[9] in 1928, on the basis of case reports assembled from the literature, estimated that multiple myeloma was twice as frequent in males as in females. Either the disease is being diagnosed in females more

frequently now than formerly, or cases reported in the literature were selected in favor of males.

AGE INCIDENCE

Incidence related to age at first diagnosis is shown in Table I. The age trend is illustrated in Fig. 1 and is compared with the age trend in death rates in the United States for 1951 and 1952.* The two curves are very similar and demonstrate a sharp association with age. In the sharpness of the age association, multiple myeloma resembles chronic lymphatic leukemia. Among the other lymphomas, lymphosarcoma and chronic myeloid leukemia show appreciably weaker associations with age (Fig. 2).

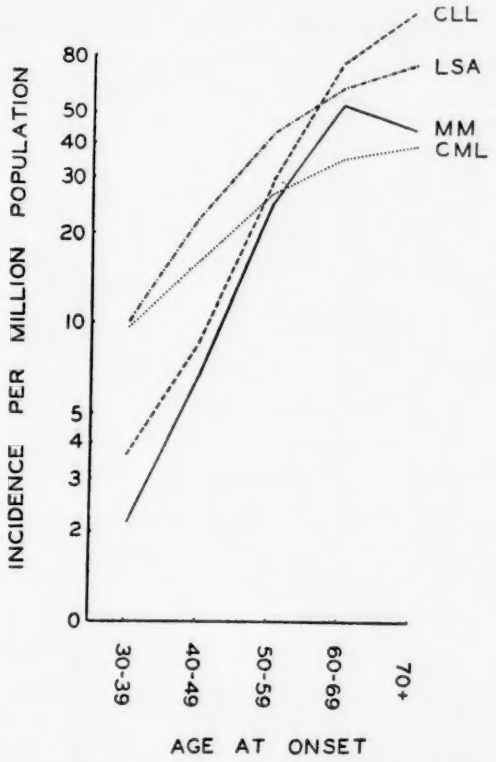

Fig. 2.—Incidence related to age at diagnosis for multiple myeloma, lymphosarcoma, chronic myeloid leukemia, and chronic lymphatic leukemia (Brooklyn, 1943-1952).

In the Brooklyn data there is a small change in the sex ratio with age. Prior to age 65 there were 83 (49.7 per cent) males among 167 patients, whereas in the two age groups after 65 years there were 52 (59.8 per cent) among 87 total patients. The difference in sex ratio between the two age periods is not significant (10.1 ± 6.7) and is probably due to chance, since no change in sex ratio with age is seen in the United States death statistics.

*The shorter period is used because no breakdown by age is given for multiple myeloma deaths in 1950.

COLOR

The numbers of white and Negro patients in the Brooklyn survey were 254 and 25, giving incidences of 10.0 and 13.3 per million per annum, respectively. The Negro population is appreciably younger than the white: standardization of the Negro rate to the age distribution of the white population raises the Negro rate to 24.5 per million—more than twice the rate in whites. The number of Negro patients in the Brooklyn material is too small for further analysis.

TABLE I. INCIDENCE OF MULTIPLE MYELOMA IN WHITES RELATED TO SEX AND AGE AT DIAGNOSIS, BROOKLYN, 1943-1952

AGE (YEARS)	NUMBER OF PATIENTS			INCIDENCE PER MILLION PER ANNUM		
	MALE	FEMALE	TOTAL	MALE	FEMALE	TOTAL
0-29	0	0	0	0.0	0.0	0.0
30-34	1	0	1	1.0	0.0	0.5
35-39	4	4	8	4.0	3.6	3.8
40-44	3	6	9	3.1	5.9	4.5
45-49	8	8	16	9.1	8.9	9.0
50-54	15	19	34	18.1	22.9	20.5
55-59	22	18	40	32.2	26.9	29.6
60-64	30	29	59	54.7	53.2	53.9
65-69	28	19	47	69.7	43.7	56.2
70 and Over	24	16	40	53.5	29.5	40.4
Total	135	119	254	10.8	9.2	10.0

TABLE II. AGE-SPECIFIC DEATH RATES FROM MULTIPLE MYELOMA BY SEX AND COLOR, UNITED STATES, 1951-1952

AGE (YEARS)	MALE		FEMALE		TOTAL	
	WHITE	NONWHITE	WHITE	NONWHITE	WHITE	NONWHITE
0-24	0.0	0.0	0.0	0.0	0.0	0.0
25-29	0.4	0.0	0.5	0.7	0.5	0.4
30-34	1.1	0.0	0.5	1.6	0.8	0.8
35-39	2.1	1.8	1.8	1.6	2.0	1.7
40-44	5.0	9.6	3.2	8.0	4.1	8.8
45-49	10.6	13.2	9.8	14.9	10.2	14.1
50-54	22.0	37.1	17.0	33.0	19.5	35.1
55-59	36.2	59.0	26.6	41.4	31.3	50.2
60-64	50.1	68.7	33.7	23.8	41.8	46.3
65-69	66.6	94.3	44.3	37.1	55.1	65.7
70-74	59.7	39.7	41.6	23.1	50.1	31.3
75 and over	50.7	26.5	25.7	17.7	36.9	22.0
Total	11.36	10.65	8.16	6.72	9.74	8.63
Total—age standardized*	11.36	14.29	8.16	9.07	9.74	11.73

*Standardized to the age distribution of the white population.

In United States death statistics, this racial difference is in the same direction but is less marked. For 1951 and 1952 combined, the age-standardized death rate in nonwhites was 11.7 per million compared with 9.7 in whites.

In Table II the white-nonwhite difference evident in United States statistics is examined in relation to sex and age. The difference between whites and nonwhites is more marked for males than for females. The percentage excess of the age-standardized nonwhite rate over the white rate is 26 per cent for males and 11 per cent for females. It is also evident from Table II that the nonwhite excess affects the younger age groups in particular. In fact, after age 70 in males and age 60 in females, rates are higher for whites than for nonwhites (Fig. 3).

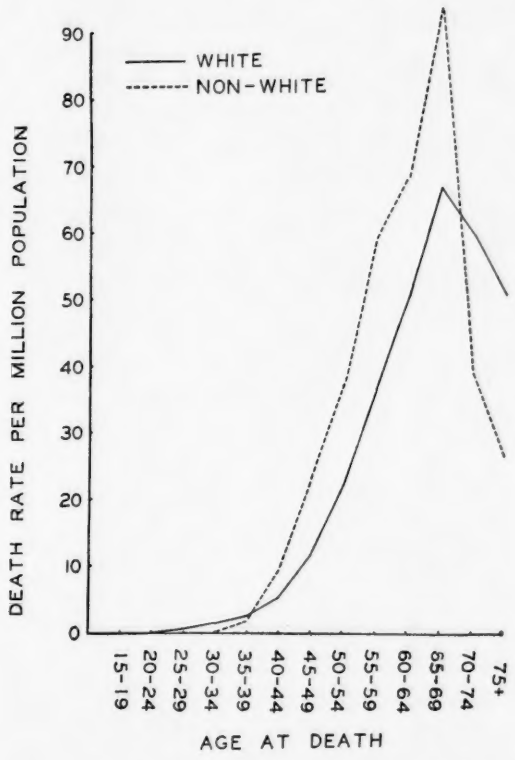

Fig. 3.—Death rate from multiple myeloma in white and nonwhite males (U. S. A., 1951-1952).

This racial relationship is one feature of the epidemiology of multiple myeloma which cannot be explained on a diagnostic basis. The difference seen in the United States data (20 per cent excess nonwhite over white) may well be a considerable understatement of the difference in risks experienced by the two groups. Diagnosis of multiple myeloma is probably very deficient in nonwhites in certain states in which the average income of the nonwhite population is low. With respect to the noted changes in the white-nonwhite ratio with age (Fig. 3), it seems possible that, when diagnosis is deficient, the deficiency

may affect the older age groups particularly. For these reasons it is felt that the real difference in risk may well approximate that observed in the Brooklyn data (100 per cent) even though the numbers on which this estimate is based are small.

Dorn and Cutler,[10] in their survey of morbidity from cancer in 1947 in ten metropolitan areas of the United States, noted that plasma cell myeloma constituted 7.5 per cent and 18.4 per cent of the lymphoma-myeloma group of diagnoses in whites and nonwhites, respectively. This is not, of course, an index of relative risks in the two groups. On the basis of the data presented by these authors, incidence rates in whites and nonwhites were 6.8 and 10.0 per million, respectively. Since the nonwhite population was considerably younger than the white, this differential would be increased by standardization for age. This maneuver is not possible with the data presented. No immediate explanation of the high rate in Negroes offers itself. Apart from its implication in the etiology of this disease, the feature is interesting because in this respect multiple myeloma differs from leukemia and all the other lymphomas, which uniformly show higher rates of diagnosis in whites than in Negroes.[7,11]

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TABLE III. DEATH RATES FROM MULTIPLE MYELOMA IN SELECTED COUNTRIES

COUNTRY	NUMBER OF DEATHS	ANNUAL DEATH RATE			TOTAL—AGE STANDARDIZED†
		MALE	FEMALE	TOTAL	
U.S.A. (white)	2,713	11.4	8.2	9.7	9.7
Canada	220	8.9	6.3	7.7	8.9
Denmark	111	12.9	12.9	12.9	12.2
Sweden**	85	12.1	11.7	11.9	10.3
Norway	115	21.5	13.1	17.4	16.4
Finland***	35	1.5	4.1	2.9	3.3
England and Wales	640	7.5	7.1	7.3	6.2
Scotland*	153	8.1	6.9	7.5	6.8
Netherlands	184	9.0	8.7	8.9	9.7
Switzerland	118	12.6	12.0	12.4	11.3
Italy	156	2.1	1.5	1.8	1.8
Australia*	159	5.0	4.3	4.7	4.9
New Zealand*	64	7.7	9.4	8.6	8.4

*1950 through 1953; **1952; ***1951-1953; all others 1951-1952.

†Standardized to the age distribution of the U. S. white population. Data obtained from the World Health Organization's Epidemiological and Vital Statistics Report.[6]

DEATH RATES IN OTHER COUNTRIES

Leukemia death rates in certain other countries, calculated from data published by the World Health Organization, are shown in Table III. The final column of this table shows the death rates standardized to the age distribution of the United States' white population. Differences between countries are marked, but it is of course in this area of geographic variation that differences in diagnosis are likely to be greatest. The most interesting feature of the table

is the high death rate noted in Norway. Although high in both sexes, the rate in Norway is particularly high in males, which suggests the possibility of an occupational hazard in this country. Two other Scandinavian countries—Denmark and Sweden—also show high rates, which in these countries affect both sexes.

SUMMARY

A survey of hospital records and death certificates yielded records of 279 residents of Brooklyn diagnosed as having multiple myeloma in the period 1943 to 1952. The mean annual incidence was 10.0 per million. During the last four years (1949 to 1952) the annual incidence in Brooklyn was 14.1 per million. United States death statistics gave a death rate from multiple myeloma of 8.9 per million during the same four years.

Corrected sex ratios were 54.0 per cent (Brooklyn) and 55.4 per cent (United States). The association of multiple myeloma incidence with age is sharper than that of any other lymphomatous disease except chronic lymphatic leukemia.

The incidence of multiple myeloma is higher in nonwhites than in whites. The excess risk experienced by the nonwhite compared to the white population is probably closer to 100 per cent (estimated from Brooklyn data) than 20 per cent (estimated from United States death statistics).

Death rates from multiple myeloma in a number of other countries are calculated from data published by the World Health Organization.

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For access to case records, we are indebted to the medical, administrative, and record room staffs of many Brooklyn and other New York City hospitals, a list of which has been published elsewhere.[8]

We are also greatly indebted to the Board of Health of New York City for permission to review death certificates, and to the Bureau of Vital Statistics of the Department of Heath for providing tabulated information.

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REHABILITATION OF THE LONG-TERM RESPIRATOR PATIENT

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INTRODUCTION

RECENT developments in the prophylaxis of poliomyelitis will significantly alter the epidemiologic importance of this disease entity. The effectiveness of antipoliomyelitis vaccine against paralytic poliomyelitis has unquestionably been demonstrated,[1,2] and it is to be hoped that the epidemics which resulted in death and serious disabling neuromuscular syndromes will no longer be important clinical problems.

However, medical responsibility is still required for some 68,000 patients in this country with varying degrees of disability, as well as for the approximately 500 seriously impaired patients with neuromuscular residua and respiratory insufficiency at present in the thirteen specialized Respirator Centers in the United States.* The value of the Centers has been demonstrated, since there has been a marked reduction in mortality due to acute poliomyelitis.[3] Once the acute phase is safely passed, with its dramatic emphasis on the saving of life, a most difficult and complicated situation is presented which can be effectively approached only by multidisciplined management.

The principles and practices of rehabilitation, with emphasis on the "team approach" to the "whole" patient, are needed to care for this type of patient. Indeed, management here epitomizes contemporary rehabilitation medicine,[4] since not only do the neuromuscular and other organ systems command the attention of the medical and coprofessional team, but management of a vital function, respiration, often becomes a paramount problem. It is probable that nowhere in rehabilitation practice does the definitive medical management of the patient play as important a role, since constant and meticulous attention must be paid to a number of organ systems which frequently become secondarily involved as the result of prolonged immobilization. There are usually required an internist, pediatrician, physiologist, rehabilitation specialist, otorhinolaryngologist, orthopedist, anesthesiologist, psychiatrist, and, for nonmedical problems, the entire

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*Much of what is said here applies not only to poliomyelitis, but as well to other conditions requiring even brief respirator care.

spectrum of the coprofessional team including nurse, physical and occupational therapist, clinical psychologist, social service worker, recreational director, teacher, and vocational counsellor. To paraphrase Sir William Osler's remarks—to be familiar with the management of the long-term respirator patient is to know rehabilitation medicine.

It is the purpose of this paper to outline a scheme of rehabilitation for this type of patient, indicating the medical, physiologic, psychologic, social, home care, educational, and vocational aspects.

DIAGNOSIS OF POLIOMYELITIS

It is not necessary here to present in detail any of the aspects of diagnosis or management during the acute phase of poliomyelitis. It should be mentioned, however, that there are numerous complexities in making the diagnosis and that these are certainly heightened by pressures on the physician by apprehensive relatives or friends of the patient, particularly during an epidemic. There is no available present method for making a definitive diagnosis during the early phases of the disease.

Clinical entities in the differential diagnosis include a variety of encephalitides and meningitides, infectious polyneuritis (Guillain-Barré syndrome), cerebral and spinal neoplasms and abscesses, pulmonary infections, specific muscular syndromes, and acute psychogenic disturbances such as conversion hysteria. The criteria for making a diagnosis of acute poliomyelitis will not be considered here. Fortunately, from 30 to 50 per cent of patients with clinical infection have the nonparalytic form of the disease. The actual incidence of nonparalytic disease in a given hospital experience depends upon variability of the disease, diagnostic criteria, admission policy, and thoroughness of follow-up evaluation.

GENERAL PRINCIPLES IN CARE

The principles of management in the early phases of the uncomplicated disease include constant observation of vital signs, maximal rest, management of dehydration and preservation of fluid and electrolyte balance, and positioning of the patient with gentle physical measures to relieve pain and discomfort and to minimize the extent of joint deformities. Strict bed rest for seven to ten days is indicated. The use of antibiotics and chemotherapeutic agents should be reserved for secondary infections and pulmonary complications. Confirmatory evidence of the presence of serious poliomyelitis is the supervention of respiratory muscle paralysis, impairment of deglutition, abnormalities of vital autonomic and respiratory function, and pulmonary complications such as pneumonitis and atelectasis. Evidence of respiratory muscle paralysis, the most common serious complication of poliomyelitis, is offered by absent breath sounds, fluoroscopic evidence of diminished or absent diaphragmatic and intercostal movement, and decreased vital capacity. Artificial respiration by mechanical means (to some degree) is eventually necessary in 80 per cent of all patients with respiratory muscle paralysis. It is generally agreed that the early, judicious, and intelligent use of mechanical respiratory aids is salutary.[5]

The details of the different varieties of mechanical equipment will not be considered here. In all instances, however, these are utilized to move air in and out of the lungs. Mechanical equipment for respiratory aid has been highly developed and includes the tank, cuirass or chest, and rocking bed varieties. In addition, accessory equipment such as positive pressure inhalation and cough and aspiration devices may be required for the adequate maintenance of respiratory function. All members of the management team should be thoroughly familiar with their use.

The purpose of management in the acute phase of paralytic poliomyelitis is to maintain life and to prevent respiratory, gastrointestinal, skeletomotor, nutritional, urologic, and other complications such as decubitus ulcers, contractures, deformities, and nephrolithiasis, which would seriously hinder subsequent rehabilitation management. An important consideration is to establish and maintain good rapport with the patient and his family, since acceptance of the mechanical device for maintenance of a vital function is of critical psychologic importance. This requires the coordinated approach of the rehabilitation team in all phases of the disease.

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PHYSIOLOGIC PROBLEMS

The difficulties in managing patients with poliomyelitis are considerably increased when respiratory muscles are paralyzed. Respirators of any type are at best inconvenient and cumbersome and, unless the patient has the ability to breathe unaided for several hours, the respirator will seriously limit his activities and retraining program. A patient may be capable of breathing unassisted for several hours at rest, but activity or illness may sharply decrease this time period. It is, therefore, necessary to assess the degree of respiratory insufficiency in each patient and to project rehabilitation goals for the patient consistent with respiratory limitations.

In evaluating patients with respiratory muscle weakness, three questions must be answered: First, Is the patient's ventilation adequate to meet his metabolic requirements of the moment (whether in the respirator or unassisted)? Second, What type of respirator should the patient use? Third, For what length of time can the patient safely be allowed to breathe without respirator assistance?

Simply stated, the purpose of respiration is ventilation of the pulmonary alveoli, with the provision of oxygen and the removal of carbon dioxide.

Although many other factors are involved in its control, ventilation is so regulated under most conditions as to maintain a constant partial pressure of carbon dioxide (and hence carbon dioxide concentration) in the pulmonary alveoli. In evaluating the adequacy of ventilation, therefore, whether of a patient in the tank or of an unassisted patient suspected of developing respiratory muscle weakness, or fatigue, the alveolar carbon dioxide concentration should be measured, a process requiring specialized equipment. Fortunately, it is possible to obtain a reasonable estimate of the adequacy of ventilation by use of a nomogram,[6] which gives the desired tidal volume if the respiratory rate and the weight of the patient are known. It must be kept in mind, however, that many factors may increase the ventilatory requirements, such as apprehension, exertion, and fever. Once the acute phase of poliomyelitis is passed, however, the patient himself is

the most sensitive guide to the regulation of ventilation and will quickly complain of insufficient ventilation when this is present.

By careful attention to ventilatory requirements based on measurement of ventilation, hypoventilation can be avoided in most cases. When it occurs, it is manifested clinically by the signs and symptoms of carbon dioxide retention, i.e., dyspnea, use of accessory muscles of respiration, headache, flushing, sweating, tachycardia, tachypnea, and rise in blood pressure. Cyanosis is a late sign of hypoventilation and indicates that ventilation has reached a dangerously low level, with incipient carbon dioxide narcosis, hypoxia, and respiratory acidosis.[7]

Hyperventilation is frequently found after the acute phase of illness; this probably results from maintenance of previous high tank pressure in patients whose metabolic requirements have decreased with the passing of fever, muscle tightness, excessive mucus secretions, and other factors related to the acute stage. Fixed low blood concentration of carbon dioxide may result.

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The correction of ventilation to lower levels may be difficult, but daily reduction of respirator pressures by small decrements, together with mild sedation, will usually be effective. The dangers of hyperventilation in the acute phase are generally less than those of hypoventilation. However, increased ventilation associated with low blood carbon dioxide content may impair the patient's capacity for unassisted breathing.

REMOVAL FROM RESPIRATOR

Removing the patient from the tank respirator is one of the first steps in the rehabilitation of the patient with respiratory muscle weakness. The advantages of the cuirass respirator or rocking bed over the tank respirator in nursing and in rehabilitation care are obvious. It is easiest first to accustom the patient to the cuirass respirator over a period of several days while he lies in the open tank respirator; with the cuirass respirator in operation, the patient can then be transferred to a hospital bed or rocking bed; if the latter, the rocking bed can be subsequently started as the cuirass respirator is stopped. In this way, it is possible gradually to accustom the patient to different types of equipment. Devices supplying intermittent positive pressure through a face mask are also useful for maintaining respiration during transfer from one respirator to the other. In the acute phase of poliomyelitis, cuirass respirators, rocking beds, or respirators supplying intermittent positive pressure to a tracheotomy tube have been used in place of the whole body tank respirator; here the "weaning" process is obviously simplified.

The choice of respiratory aid to which the patient should be "weaned" from the tank respirator must be governed by practical considerations such as comfort, the adequacy of ventilation, and availability. In general, tank respirators and respirators supplying intermittent positive pressure to a tracheotomy tube give about 50 per cent more ventilation for a given pressure setting than the cuirass type respirators; the maximal ventilation provided by the rocking bed is generally somewhat less than that provided by chest respirators, but this may vary greatly from one patient to another.

Rehabilitation is, of course, facilitated if the patient is able to breathe unassisted for an appreciable period. In determining whether and to what extent

a patient with respiratory muscle weakness needs respirator assistance, the vital capacity is a useful measurement. In the acute phase, as progressive paralysis involves the muscles of respiration, the vital capacity begins to decrease. When it falls to 40 or 50 per cent of the predicted value,* it is desirable to accustom the patient to the tank respirator. If the vital capacity falls to 25 per cent of the predicted normal value, the patient probably will require a respirator full time. In convalescence, as the vital capacity increases, the patient's ability to breathe without respirator assistance will also increase. In our experience, patients with a vital capacity less than 10 per cent of the predicted normal value are able to breathe unassisted for only a few minutes, whereas those with vital capacities above 30 per cent of predicted normal value are eventually able to go from days to months without respiratory aids if they do not perform activities which exceed their respiratory reserve.

A more exact assessment, however, is needed to determine how long the patient may safely go without respiratory aids. This is provided in the unassisted breathing tolerance test[8] in which the respiratory rate, pulse, blood pressure, and vital capacity are followed at intervals after removing the patient from the respirator. At the onset of fatigue, the pulse, blood pressure, and respiratory rate will show a persistent upward trend, while the vital capacity will fall. In our experience, prolonging the period of unassisted breathing to the point of acute respiratory distress serves no useful purpose and increases the patient's attitude of apprehension and discouragement toward the "weaning" process.

In patients with a very short unassisted breathing tolerance time, the use of glossopharyngeal or "frog" breathing[10,11] can be a valuable adjunct. Here the tongue and pharyngeal muscles are trained to force the air into the lungs in rapid, successive movements, expiration being passive. After mastery of this maneuver, patients are often able to breathe by this method alone for several hours.

The importance of complex psychologic factors in the success of the "weaning" program is frequently striking. Apprehension, insecurity, lack of motivation, and dependence are frequently impediments. Attempts to force the rapid "weaning" of such patients is both unwise and usually unsuccessful. Psychiatric management of emotional factors retarding the "weaning" process has been helpful in some patients. These facts play a significant role in setting the pace of the rehabilitation program.

These principles are valid with some modifications for the patient requiring respiratory aid in such entities as pulmonary emphysema, bulbar involvement of multiple sclerosis, barbiturate intoxication, and certain neurosurgical conditions. In such instances, the intelligent use of mechanical respiratory aid may be lifesaving.

Many patients have tracheostomies performed in the acute phase of bulbar poliomyelitis because of poor coordination of swallowing and breathing movements or difficulty in handling respiratory secretions. In the postacute phase, it is our feeling that fewer respiratory complications arise if the tracheostomy is

*Predicted vital capacity (in c.c.) can be estimated from the formula:

Predicted normal vital capacity (in c.c.)[9] = 25 × height in cm. (males).
= 20 × height in cm. (females).
= 200 × age in years (children).

allowed to close early, provided there is normal pharyngeal, glottic, and vocal cord action. There are, however, differences of opinion on this subject. Many physicians prefer to leave the tracheotomy tube in place until ventilatory capacity is adequate, in order to facilitate removal of secretions and to permit the use of respiratory devices applied to the tracheotomy tube.

RESPIRATORY TRACT INFECTIONS

The development of upper respiratory infections in the patient requiring respiratory aid, particularly if cough is ineffective, is a matter of serious consequence, since this normally benign syndrome frequently leads to increased mucous secretion, pneumonitis, and atelectasis. As a result, stringent prophylaxis should be practiced. All visitors and staff with symptoms suggestive of upper respiratory infection should be prevented from coming into contact with the patient. It has been suggested that the administration of gamma globulin to respirator patients will protect against secondary invaders. The use of positive pressure, deep breathing, mechanical aids to coughing, expectorants, and humidification of inspired air have also been suggested. Should atelectasis and pneumonitis supervene, vigorous antibiotic therapy as well as bronchoscopy may be required. Increased respiratory tract secretions may also occur after inhalational anesthesia and as a result of emotional influences. Pneumonia may also follow aspiration of ingested food, particularly in patients with residual paralysis of the pharyngeal musculature. The occurrence of atelectasis or pneumonia usually increases ventilation requirements and tank respirator care becomes necessary.

GASTROINTESTINAL PROBLEMS

A frequently observed syndrome in respirator patients is acute gastric dilatation. The pathogenesis of this entity is obscure, although it has been suggested that psychogenic factors may play an important role in its development. In addition, it is frequently seen after acute renal colic and its onset is facilitated by increased negative pressure settings on the respirator. The upward pressure on the diaphragm by the enlarged viscus further encroaches on the respiratory reserve and many such patients require tank care. The use of Prostigmin and its derivatives has been suggested by some, but the most effective procedure in our hands has been gastric intubation, suction by the Wangensteen technique, and replacement of electrolytes and fluids by means of parenteral therapy. All such procedures can be effected with the patient in the tank respirator through slight modifications in the respirator walls. Other important gastrointestinal complications are constipation and fecal impactions. These appear to initiate acute exacerbations of urinary tract infections as well as acute gastric dilatation.

In the prevention of constipation, the goal is regular periodic evacuation with minimal resort to laxatives and enemata. The patient should be placed on a three-day cycle of gradually increasing stimuli (laxatives and suppositories); should be offered the bedpan daily at the same hour; and this routine should culminate in an enema on the third day if no bowel movement has occurred. Such a regimen frequently leads to a normal bowel pattern. The addition of raw fruit and maintenance of a high fluid intake assist in minimizing the frequency of im-

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pactions. Defecation may be aided through the use of a cuirass respirator over the abdomen with a high positive pressure setting. It has been recently suggested that wetting agents, such as Tween 80, orally administered, may be effective in prevention of constipation.

CARDIOVASCULAR PROBLEMS

Hypertension may occur during and following the acute phases of poliomyelitis. In the majority of cases, the hypertension gradually decreases during the first year without antihypertensive therapy. In occasional instances, elevation of the blood pressure persists. The cause of the hypertension is obscure, although it has been thought to be of central nervous system origin.

Electrocardiographic changes may persist in the postacute phase of poliomyelitis. Most frequently, there are T, QRS, P wave, and axis changes. Their significance is uncertain and in most instances they are not associated with chemically discernible abnormalities in the blood. Myocarditis is believed to be frequently, if not always, associated with severe cases of poliomyelitis and may be the cause of the electrocardiographic findings.

UROLOGIC PROBLEMS

In the long-term respirator patient, complications in the urinary system assume major significance. This is similar to experience with paraplegic patients in rehabilitation centers. Predisposing factors for abnormal calcium deposition include prolonged immobilization with resultant demineralization and increased calcium excretion, urinary tract infections, constipation, oliguria, and stasis. Preventive measures should include adequate fluid intake to obtain urine specific gravities of 1.010 to 1.020, determination of presence of stones by means of serial flat abdominal x-ray films, avoidance of high vitamin D intake, and repeated urinalyses and urine cultures to allow for early and adequate chemotherapy. In addition, the patient should be mobilized as early as feasible, using physical therapy, frequent body positioning, and skeletal weight-bearing by means of the tilt table. Periodic renal function studies should also be performed every two to three months.

Chronic urinary tract infections presumably follow urine stasis and catheterization in the acute phase. Constipation and fecal impaction may also be contributing factors. Hypercalciuria (which may continue for as long as twelve months in patients with extensive paralysis), urine stasis, and chronic urinary tract infection contribute to the formation of urinary stones in the postacute phase. Mandelamine is useful in controlling symptoms and in maintaining an acid urine in chronic pyuria. High fluid intakes, with urine outputs in excess of 2 liters per day, are desirable. The use of salicylic acid in controlling urolithiasis has been recommended and appears promising,[12] although the effectiveness of salicylates has not been adequately demonstrated. Ureterolithotomy is essential where ureteral blockage by stones occurs or threatens. Delay in operation may seriously compromise renal function. Expert urologic supervision is mandatory.

ORTHOPEDIC PROBLEMS

The orthopedist should see the patient early in the course of his disease, with careful follow-up throughout the entire extent of the convalescent phase.

Surgical intervention is frequently concerned with procedures upon connective tissue and muscle when conservative measures such as neuromuscular re-education, stretching, and splinting fail to result in maximal function or adequately minimize the effect of deforming stresses. Most frequent offenders in the latter category are the iliotibial band, Achilles tendon, and abdominal musculature. Especially important in a growing child is prevention of deformities. In general, the effectiveness of a surgical procedure depends on the functional capacity to take advantage of the result; for example, a probably successful opponens transplant may be wholly ineffective functionally in the absence of common extensor function. It is necessary to estimate accurately bone age in planning orthopedic surgical procedures. Fusion and stabilization procedures are performed to aid function, enhance stability, and correct established deformities as well as to eliminate need for appliances. In selected cases, tendon transplants may be used to substitute for a lost function or to redirect a deforming force. Motor transplants should use muscle which has at least 70 per cent of normal strength. In many instances, proper combinations of stabilization and transplants may result in better function of a part than either alone. Orthopedic surgical procedures should be performed only after a suitable time interval, when no further increase in function can be expected, and only if reasonable objectives or goals for the patient are to be expected.

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PSYCHIATRIC PROBLEMS

During the acute phase of the disease process, anxiety, confusion, delirium, and, in some instances, stupor and coma are prominent features. In convalescence and with the realization of the immobilized state, passivity, regression, dependency, and negativism are prominent concomitants. In adults, guilt feelings are frequently observed. In time, this guilt may be directed outwardly and the guilt feelings are then projected as resentment and hostility to family and medical staff. In the long-term patient, seemingly inconsistent patterns of behavior may be prominent. Emotional lability, with a tendency to overact, is frequently seen. Patients of this type, with overwhelming marital and family problems superadded, frequently manifest severe degrees of depression. The psychologic readiness of the patient for indicated medical procedures must always be considered. It is essential that these problems in the patient as well as his family be managed by qualified psychiatric and clinical psychologic personnel.

PHYSICAL MEDICINE AND REHABILITATION PROBLEMS

Actual physical medicine and rehabilitation management of patients with paralytic poliomyelitis can be considered as falling into three major phases: (1) the acute phase, where primary consideration in bulbar involvement is life-saving; (2) the recovery or convalescent phase, when involved neuromuscular elements recover and the inflammatory process subsides; and (3) the chronic phase, during which there occurs adaptation to residual disability. In the early stage, judicious use of heat, passive motion, and support and positioning of the weak segments must be instituted with care, since overapplication of these measures may do more harm than good. Strenuous stretching of involved

muscles, as well as the administration of drugs such as curare, Priscoline, Prostigamin, tetraethyl ammonium compounds, and Tolserol, as well as others, are now not considered by many as desirable and, indeed, may be harmful.[13]

In the convalescent phase of the disease, management is predicated upon the basic principle of rest, with gradual introduction of activity, initiated and sustained through muscle re-education on a graded basis and guided by the degree and quality of response. Relief of pain, muscle tightness, faulty posture, and prevention of deformities are objectives. Apparatus such as splints, braces, supports, and other devices are utilized for support of weak muscles, for assistance in movement, and for prevention of deformities, as required, especially of the upper extremities. All these devices are prescribed by the physician on the basis of the patients' residual muscle and joint disabilities.

A cardinal principle throughout this phase is that overuse of weakened musculature causes decrease in muscle strength. However, increasing activity should be a prime objective and should be skillfully supervised so that fatigue is prevented. While there have been a number of recommendations for systems of muscle re-education, as well as techniques of introducing graded activities, there is unanimity of opinion regarding the basic principle of remaining below the fatigue threshold. The use of a tilt table with careful supervision is also of value since important homeostatic mechanisms, especially in the cardiovacular system, can be restored toward normality. It may also be of value in that osteoporosis may be diminished.

Serial manual muscle testing (MT), range of joint motion testing (ROM), and recording of performance of activities of daily living (ADL) provide means of evaluating progress after base line determinations have been made. Close observation of such programs is required to obviate the development of scoliosis and contractures. If improvement occurs, supportive, assistive, and corrective apparatus may gradually be removed. When sufficient recovery does not develop, it may be necessary to continue their use for alignment, support, and stability.

It is at this juncture that orthopedic procedures may be of great value. Weakened muscles can be strengthened to a certain degree by exercises of the progressive resistive type. When this fails, function may be enhanced by tendon transplants and the use of functioning muscles. Surgical procedures for joint stabilization are usually deferred beyond adolescence since these are irreversible and may interfere with growth.

Scoliosis can be a major deformity following paralytic poliomyelitis in childhood. It occurs as the result of muscle imbalance. It is a good policy for every child who has had poliomyelitis to have x-rays of the spine twice a year for a period of at least ten years. Spinal fusion has been stated as being the only available method for maintaining correction in paralytic scoliosis as well as for the prevention of further complications in severe, progressive cases.

When the patients' attainments become static, adaptation to the disability ensues. It can be safely said that return of further muscular function is unlikely after approximately eighteen months from the acute phase of the disease. Between 50 and 75 per cent of that muscle function which returns will have returned in six to nine months. For those in whom considerable functional capacity has been lost, a large variety of self-help devices, both mechanically and electroni-

cally activated, is available. These range from remote control relays operated by breathing, chin or finger motion, and electric typewriters, dictating machines and other equipment; and for those with lower extremity involvement, self-powered electrical wheelchairs.

Experience has shown that much can be done with aid of simple mechanical devices, which allow the patient to perform activities of daily living independently or with a minimum of assistance from others. Many of the devices for hand activities are of the one-hand variety, e.g., articles for dressing that circumvent fastenings requiring the use of both hands. Buttons and snaps are easier to manage than zippers. The same is true for pretied shoe laces and neckties. For personal hygiene, there are special suction cup hand brushes. For the disabled housewife, there is the suction cup bowl to allow for one-handed egg beating. There are numerous other devices which can be of great value to the disabled patient.*

In younger patients of school age, the educative process should be continued by means of special teachers. An important member of the rehabilitation team is the occupational therapist who can, by means of prevocational explorations, in conjunction with aptitude testing by the clinical psychologist, determine vocational potentialities for such patients. The utilization of community agencies, such as Vocational Rehabilitation Divisions, among others, can be of great value in vocational planning.

If a proper home environment exists, many patients, even though severely disabled, can be discharged to a home care program with respiratory aids and assistive devices. Such programs can be lastingly effective only if medical, coprofessional, and family interest is continued. Home care planning is an extremely important step in the resocialization program for the patient, since it is the first phase in the return to the family unit and thus eventually to community living.

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SUMMARY

Changing medical concepts, created by the evolution of newer techniques in the prevention of disease processes, and the management of severely disabled patients, indicate the value of a dynamic approach toward fulfillment of our responsibilities. This is illustrated by the rehabilitation management of the long-term respirator patient, who may be considered a prototype of disabling chronic disease.

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THE REDUCTION OF ANXIETY IN A HOME CARE SETTING

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INTRODUCTION

THE organization and functioning of the Home Care program of Montefiore Hospital have been described previously[1,2] and specific applications to cancer patients[3,4] and cardiac patients[5-7] have been noted. At the time the program started, it was felt that the services offered the home-bound should be equivalent to those in the hospital so that no patient could feel that an inadequate alternative had been provided. Accordingly, a team whose members paralleled the important personnel caring for the patient in the hospital was formed. The team consisted of the doctor and consultants, the social worker, the nurse, occupational therapist, and physical therapist. The contributions that each make have been detailed elsewhere. If an adequate evaluation is done of the referrals to the program, no significant difficulty is encountered in the patient's transition from hospital to home. Rather, the original fear that the patient would be reluctant to go home has often been reversed in that patients may be loath to return to the hospital. It has been possible to follow patients for years in some instances, both in the hospital and at home, and observe the patients' reaction to each of their environments. We have also been able to draw a contrast with the patient's course before Home Care was available and evaluate some of the psychologic impact of our program.

Of singular interest have been the patients who did badly before the advent of Home Care and with whom notable therapeutic results occurred after treatment in our program. Improvement has been seen after months of diligent effort which in hospital wards seemed fruitless. Such patients were referred for Home Care in the belief that their disability was both chronic and intractable. A recent instance is that of an 18-year-old boy with severe, generalized, rheumatoid arthritis. The patient exhibited marked atrophy of the musculature, was unable to walk, and continued to be bedridden despite major efforts to mobilize him. In one hospital he received combined medical and psychiatric treatment on a "psychosomatic" pavilion, since it was recognized that depressive and other emotional features were present. Following transfer to Montefiore Hospital, the patient received the usual antirheumatic measures, combined with extensive physical therapy; in addition, a great deal of unusually personalized interest was extended him. Despite all this, the boy remained completely

disabled and nonambulatory for a ten-month period. At the time of his evaluation for Home Care, he had been in four major hospitals for two years. He was regarded as a bedridden nursing problem for whom the only community alternative to Home Care was chronic institutionalization. Contrary to expectation, the boy did remarkably well at home. After a time, he performed maneuvers that had been deemed impossible, and eventually became ambulatory on crutches.

The chief members of the Home Care team who treated this boy were the nurse who visited almost daily in the beginning, and the physical therapist who visited several times weekly. They both adopted kindly, warm, but firm attitudes in the trying and painful period of rehabilitation. Although in the hospital no one seemed able to develop a durable relationship with the boy, therapeutically useful relations involving the nurse and physical therapist were established in the home setting.

Cases similar to this have emphasized the unique potentiality of the Home Care setting and illustrate the fact that the patient's course on Home Care is not necessarily predictable from past medical experiences. Many patients spontaneously remark that they feel better at home than in the hospital. Even casual observation often reveals that their spirits are higher, that they eat better and feel stronger. For a patient with far-advanced cancer or severe chronic congestive failure, improvement of this sort may not have significant impact on the process. Because of the criteria used for admission to our program, most patients fall into such a far-advanced category. In the two patients to be described, however, we see disease processes still capable of major modification. This paper will describe some of the factors implicit in Home Care therapy that distinguish it from treatment in the home in standard practice. For reasons to be discussed, it is our belief that the results of Home Care treatment seen in the following two cases are to be largely ascribed to improvement in the patients' sense of security.

CASE REPORTS

CASE 1.—F. B., 56 years old: Rheumatic heart disease; mitral stenosis and insufficiency; paroxysmal arrhythmias with pulmonary edema; supraventricular tachycardia, auricular flutter, auricular fibrillation, nodal tachycardia.

Prior to entering Home Care, this patient had many stays on an overnight ward plus the following hospitalizations: Nov. 29 to Dec. 29, 1941; March 29 to April 10, 1943; May 17 to June 10, 1946; July 18 to Aug. 11, 1946; Jan. 16 to 19, 1947; June 5 to July 19, 1947; Oct. 15 to 30, 1947; March 13 to 15, 1948; Sept. 3 to Oct. 4, 1948; Oct. 9 to 24, 1948; Nov. 15 to 16, 1948; Nov. 22 to Dec. 24, 1948; Dec. 24, 1948 to May 27, 1949. These totaled 13 hospitalizations (348 hospital days).

Previous Medical History.—This patient had typical attacks of rheumatic fever at ages 9 and 11, treated with bed rest. She was told of heart murmurs at the age of 27. She had an uneventful full-term pregnancy at the age of 34. Her first hospital admission for cardiac disease was in November, 1941, at the age of 42, at which time she complained of dyspnea, orthopnea, and fatigue of five days duration. The significant findings consisted of cardiac enlargement, the murmurs of mitral stenosis and insufficiency, a ventricular rate of 148, and râles over the lower half of both lung fields. An electrocardiogram revealed auricular flutter with a 2:1 block. She was rapidly digitalized, and during the next three days the electrocardiogram revealed auricular fibrillation with rates of around 130. She finally reverted to regular sinus rhythm, rate in the 80's,

one week after admission. She was discharged on digitalis and during the next year was seen 9 times in the outpatient department, where regular sinus rhythm without evidence of failure was found. In the summer of 1942, while out of the city, she had two attacks of tachycardia which lasted about twenty-four hours and ceased spontaneously. The next hospitalization in March, 1943 was again for pulmonary edema due to paroxysmal auricular fibrillation. There were 10 further hospitalizations between 1946 and 1948, as noted above. Each of these was for similar complaints of palpitations and dyspnea. Electrocardiogram studies revealed a variety of arrhythmias, and clinically she was in pulmonary edema with all of them. No evidence of rheumatic activity was uncovered. During one hospitalization, her ventricular rate ran between 120 and 170 for five days. She was treated with quinidine and digitalis to toxicity, and with magnesium sulfate. In one of her 1948 hospitalizations, while in an oxygen tent, she was given a dose of quinidine following which she had a convulsion and was pulseless for 2½ minutes. An electrocardiogram revealed idioventricular rhythm. Following her twelfth hospitalization in December, 1948, the patient was transferred to Montefiore Hospital. During the six months on our ward, she had repeated bouts of tachycardia with pulmonary edema. The clinical and therapeutic experiences encountered at the preceding hospital continued here. At various times she was treated with quinidine and strophanthin, sedatives, morphine, and potassium. Mercurials were given for acute failure precipitated by the arrhythmias.

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Home Care History.—The patient was first seen at home on June 4, 1949, at which time she was off digitalis and taking quinidine 0.1 Gm. three times a day. The blood pressure was 134/78, pulse rate 80, regular sinus rhythm. The heart was enlarged to the left, its border extending 3 cm. past the midclavicular line. There was an apical systolic thrill and at the apex a typical rumbling, presystolic murmur with a loud systolic murmur. The liver was 3 fingerbreadths below the costal margin. Forty-eight hours later, after administration of a mercurial diuretic, she was seen at the height of one of her attacks. She was wheezing with an apparently regular cardiac rate of 160. There were rhonchi and fine moist râles over both bases and she was markedly dyspneic at rest. There was no slowing of the ventricular rate with carotid sinus pressure. The patient was given ouabain 0.2 mg. intravenously, and the cardiac rate dropped to 80 within a few minutes. Two further attacks occurred two and eight days later. On the latter occasion, the Home Care physician on emergency call was sufficiently alarmed over her pulmonary edema that he rehospitalized her. She was readmitted to the Home Care program two weeks later and on the first visit to her home was found to have a ventricular rate of 140 and a pulse rate of 90. She was evidently in paroxysmal auricular fibrillation. A number of further attacks with ventricular rates ranging from 140 to 180 occurred between Aug. 31, 1949 and Nov. 27, 1950. On different occasions, the attacks were treated with digitalis derivatives, sedation, and morphine. For the past four and one-half years, there have been no further bouts of paroxysmal arrhythmias and pulmonary edema. The patient has presented chiefly problems associated with digitalis sensitivity and mild, chronic congestive failure. She was found to be easily thrown into toxicity with digitalis, exhibiting repeated coupling and short runs of extrasystoles. She has been treated for congestive failure with salt exchange resins,[4] ammonium chloride, and mercurial diuretics.

Case 2.—M. R., 63 years old: Bronchial asthma with anxiety state, previously diagnosed and treated chiefly for arteriosclerotic heart disease in failure.

This patient was never studied at Montefiore Hospital. Her previous hospitalizations were: May 1 to 26, 1952; July 15 to 28, 1952; Feb. 14 to March 18, 1953; June 10 to Oct. 24, 1953. These totaled 4 hospitalizations (211 hospital days).

Previous Medical History.—The present illness commenced in 1952 when the patient, age 60, developed an episode of severe substernal pain, without radiation, while on a bus in New York City. She was rushed to a city hospital, given morphine, which ended her pain, and had an uncomplicated course during four weeks of hospitalization. Although electrocardiograms were not diagnostic, she was regarded as having had a myocardial infarction, was told she had heart disease, and was discharged on digitalis. At home she had frequent but irregular episodes of dyspnea with substernal sensations varying from heaviness to what was described as strong pain. These varied from a few minutes to many hours in duration. The pain and dyspnea were generally associated, were not necessarily related to effort, and were more frequent at night. Her family physician saw her repeatedly on an emergency basis and treated her with mercurial diuretics. Because of

exacerbation of these complaints, she was hospitalized as noted above. The consensus in the hospitals was that she had arteriosclerotic heart disease, borderline cardiac compensation, and bronchial asthma. In addition to frequent episodes of shortness of breath during the day, she was subject to severe attacks of nocturnal dyspnea for which various emergency measures were employed, chiefly diuretics and aminophylline. Considerable difficulty was encountered in deciding to what extent her attacks were due to cardiac rather than bronchial asthma. She showed poor response to all therapeutic measures. Her weight declined to 118 pounds (normally 180-190). In the second month of her last hospitalization, a right upper lobe lung abscess developed which cleared up with prolonged antibiotic therapy. Prior to discharge her asthma worsened, and her general condition was poor. It was felt by some that she should be referred to a chronic disease institution, but the transfer was declined by the patient. Referral was then made to the Montefiore Home Care Service.

Home Care History.—The patient was seen at home for the first time on Nov. 10, 1953 approximately ten days after her discharge from the hospital. Her chief complaints were of severe shortness of breath and heaviness in the chest on attempting ambulation, and moderately severe dyspnea at night. She was on digoxin (0.25 mg. a day), epinephrine by inhalation, and rectal instillations of a prescription which included aminophylline, Demerol, and a barbiturate. The physical examination, similar to that described in her hospitalizations, revealed moderate dyspnea and evidence of severe weight loss. The blood pressure was 130/70. The heart was not enlarged. The tones were of fair quality with regular sinus rhythm at a rate of 74. There was a soft, apical systolic murmur. There were widely scattered rhonchi and wheezes over the lung fields. The liver was not enlarged and there was no peripheral edema.

The patient was visited initially twice a week and maintained on drugs similar to those administered in the hospital. Trial doses of mercurial diuretics, with and without aminophylline, had no significant effect on the patient's symptoms. Gradual improvement, with modest diminution in dyspnea and increase in weight and strength, were observed after two weeks. An attempt to keep her as free as possible of more severe episodes of dyspnea was made, utilizing a variety of antiasthmatic remedies such as ephedrine and phenobarbital, Aludrine, and Norisodrine by inhalation. She would respond to one or another of these for a time. Her weight gain continued. After five months on Home Care, she had gained 20 pounds, was free of symptoms much of the time, but was depressed by occasional recurrences of her dyspnea. To demonstrate to her that she was not in the grip of an inescapable disease, she was put on ACTH Gel in doses of 40 units thrice weekly, commencing about the sixth month. For a period of three months, she was entirely free of dyspnea and was very exultant. A recurrence of wheezing a few weeks after cessation of ACTH therapy depressed her profoundly, but was of brief duration. At present, the patient is on Meticorten therapy in doses of 2.5 mg. 2 to 3 times daily and is almost asymptomatic. She is off digitalis derivatives, is freely ambulatory, does all of her housework, and her weight is up to her normal 180 pounds.

DISCUSSION

For a suitable patient with chronic illness, the transferral of medical activities from the hospital into the home has not presented new problems. By the time the patient is referred to Home Care, diagnosis and treatment have usually been thoroughly evaluated by prior medical experiences. The patient will therefore be continued on the same type of drug therapy. The patients described above showed marked improvement at home without significant changes in the use of drugs. Both had intractable disease, unresponsive to the usual measures. Their illnesses were not helped in long and repeated hospitalizations nor by a variety of skilled efforts in the hospital. It would seem clear from our long period of observations that the improvement observed on Home Care was due to factors other than use of ordinarily indicated medications.

A number of factors are probably operative in the abatement of symptoms. Among them we can consider the following:

1. The home versus the hospital as a medical environment. Especially after repeated hospitalizations, many chronically ill patients begin to yearn for home despite optimal hospital surroundings. There is a time when further care in a hospital emphasizes the chronicity, tenaciousness, and apparent incurability of the illness. It is then that the patient requests or even demands that he be returned to his home, and the home increasingly becomes a symbol of familiarity and security. Doubtless many factors contribute to making the home such a refuge. The average patient, after the usual unpleasant in-hospital procedures, begins to feel at the mercy of the physicians and other hospital personnel. This concept is often behind the patient's ideas that he is "being experimented on," or "that the doctors are no good." On his return to home, however, the patient may become the dominating figure because of the special status conferred by illness. In any case, he escapes the harassments experienced in the hospital, and the threatening figures of the hospital are exchanged for the familiar members of the family. In the home it is possible to avoid thinking about one's illness and disability, a protective mechanism which is much harder to use in a hospital setting steeped in illness and, occasionally, death. In addition, patients usually regard transfer to Home Care as a step forward which carries the implication that they are not so ill that continuous hospitalization is mandatory. The anxiety-laden associations invariably linked with a hospital stay, chiefly associations of doom, disability, and death, are therefore mitigated in the home.

2. Modification and improvement of the home as a medical setting. One of the chief tasks of the medical case worker is the evaluation of the home setting and working through the patient's return with the members of the family. Where hostile and rejecting attitudes are encountered, it is generally impossible to establish a satisfactory Home Care environment, and thus the patient is rejected for social reasons. Far more frequently, however, one encounters anxiety regarding the role the family is to play, with doubts about their ability mixed with unwarranted fears of the disease process. The case worker, in consultation with the physician, therefore orients the family regarding the illness. In a variety of other ways she smooths the return home and the acceptance of responsibilities involved in patient care. For example, both our patients returned to home settings in which their acceptance was provisional. The first patient had been out of the home so frequently and for such long periods that her husband and son had worked out routines which no longer included her. Their way of life indicated to the patient that it was not anticipated that she could remain at home for any sizable period. The husband of the second patient, when first seen, said that he could no longer bear her illness, the interruptions of sleep, the many emergencies, and the financial outlay that had been going on for two years. Arrangements that had been made for her indeterminate stay in an organizational nursing home had fallen through because she was considered too ill by the home. In both families the basic relation between the sick member and others was historically good. It became possible through medical casework methods to produce more accepting and supportive attitudes. Perhaps as important as casework directed toward specific goals is the effect on the family of the repeated visits and efforts of the Home Care team. The attention and

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time given transmits to the family, just as it does to the patient, that he is a person of worth and deserving of often extensive effort. The net effect is to raise the esteem in which the patient is held and to reverse the loss of status which so frequently becomes linked with chronic disease.

3. The solution of the financial problems of the illness. Our program supplies various aids and makes contributions when indicated which relieve patients of pressing financial worries. Medical care and equipment are supplied free, if necessary, and the problems of payment for drugs, ambulances, nursing care, and the like are solved. A further boon to many patients is the subsidizing of housekeeping aid over a limited but useful range. Where our services are not sufficient, plans involving other community agencies are put into effect with the result again of not penalizing the chronically ill with financial worries. Such worries contributed to the tensions of both our patients. The first one, after a time, was repeatedly told by her husband that medical and hospital bills "would drive them to the poorhouse." When their only son graduated from high school, there was a great controversy over whether college education was financially possible in view of the continual medical expenses. All of this was perennially disturbing. A similar situation existed in the second case: at the time she was accepted on Home Care, all of the family savings had been exhausted. Thus, in addition to all the other anxieties they had experienced, both patients keenly felt that they were financial burdens to their families. With their acceptance on Home Care, the accumulating pressure of financing the illness was largely abolished.

4. The altered quality of the interpersonal relationships in the home. Care delivered into the home on a program such as ours brings to the patient a feeling of involvement with personnel interested in him and desirous of helping him. In a home setting, our services carry warm and friendly implications different from those felt in the hospital. Thus, the patient feels that a service which is delivered as a routine in the hospital is an act of generosity when performed in the home. Patients specifically have commented on the fact that the Home Care personnel may climb many flights of stairs or drive to them under poor conditions, and do this freely without being called. Patients respond to this atmosphere of friendly generosity in a positive manner with an increased desire to get well and with increased cooperativeness. The many features of the changed doctor-patient relation in a Home Care as against a hospital setting deserve exploration. Our experience indicates it to be a significant aspect of Home Care therapy.

5. The adequacy of care in the home. The patients' improvement on Home Care is to be contrasted not only with their course in the hospital but also with their previous course at home before acceptance on our program. The occasional patient who in the hospital raises questions as to the adequacy of the care that can be delivered in the home is usually reassured within a brief time. The patient finds that his physician visits at regular intervals and that all the other members of the Home Care team come as frequently as is necessary and desirable. Most of our patients previously had irregular and generally inadequate care at home: some of our cardiac patients called in doctors only when they became unbearably dyspneic. Patients with cancer similarly called

for a doctor only in a severe exacerbation of symptons or for other major manifestations. There had seldom, if ever, been any nursing care. We substitute regularly delivered for emergently delivered medical care. Although some of the doctor's visits may not result in new findings or lead to changes in therapy, they act as an important communication to the patient; thus a "routine visit" can indicate to the patient that his medical status is stable and is therefore of reassurance value.

6. Techniques of explanation and reassurance. Most of our patients, including those with repeated hospital experiences, have seldom been previously informed regarding their illness. As a consequence of ignorance, they live in fear of recurrent symptoms. Early in our experiences on Home Care, it was recognized that such anxiety led to frequent calls for home visits. Partly to avoid unnecessary requests for house calls, but more importantly to diminish the patient's anxiety, it became customary to brief the patient with respect to his symptoms and to supply suitable emergency medication. A simple conception of the cause of dyspnea was given to both of our patients. They were also told to call at once with any attack and were encouraged to telephone freely. This policy gave them a good measure of reassurance. In addition, the first patient had a series of preliminary interviews at home with a neuropsychiatrist. Chiefly, he reassured her without any formal attempt at psychotherapy. Both the social worker and attending internist also gave her direct reassurance as to the possibilities of staying at home and to the effect that improvement was to be expected.

The extent to which the factors described above will benefically affect a patient is variable, depending on the patient's illness and the extent of change introduced by Home Care. The two patients discussed here responded to these features of Home Care much as have others, but are notable only because their illness was of a type that was especially sensitive to Home Care therapy.

Paroxysmal arrhythmias and asthma are thought of by some physicians as "psychosomatic" or "somatopsychic" diseases, an abused term designating an illness in which emotional factors may be importantly operative. Neither of the patients was consciously aware of fluctuations in anxiety nor were they able to account for the disappearance of symptoms on Home Care. To what extent in-hospital psychotherapy might have helped these two women is conjectural, especially in view of the many realistically distressing events experienced at home. It becomes clear in talking to them that they were deeply involved in despair over a seemingly endless illness and in family tension bred by it. Between hospital stays, they felt unsupported and lived in fearful anticipation. So far as personality characteristics are concerned, the patients are quite different. The first is a phlegmatic, stable woman, many of whose emotional reactions to her illness seem realistic enough. The second woman, as became clear after a time, was a patient with long-standing anxiety who had nevertheless functioned well until caught up in her present illness. Once launched on their careers of recurrent symptoms and hospitalizations, all of the tension-increasing sequelae subsequently kept each of them at a high level of anxiety. In this sort of context, there was a continued maintenance of symptoms; with a diminution of tension, these essentially self-perpetuating cycles came to an end.

SUMMARY

Several cases are discussed of patients whose illnesses prior to treatment on a Home Care program were marked by intractability. Their stays in the hospital ranged from many weeks to many months, and chronic institutionalization had been actively considered. In a Home Care setting, a striking improvement occurred. The case histories illustrate that an alternative to a hospital care such as a Home Care program affords may have unique therapeutic aspects. Some of the factors contributing to improvement are described and the conclusion reached that the patients were benefited because of a decrease in their anxieties.

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Clinical Conference

A CLINICAL CONFERENCE ON CHRONIC PERICARDIAL EFFUSION

Its Differential Diagnosis and Treatment

Conducted by Dr. Martin G. Goldner and Edited With the Assistance of Dr. Irving G. Kroop

Brooklyn, N. Y.

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Dr. Martin G. Goldner: The patient to be discussed at this conference presents the diagnostic and therapeutic problems of chronic pericardial effusion. His signs and symptoms and the clinical course of his disease illustrate the differential diagnosis between myocardial and pericardial disease and bring into focus the medical and surgical modalities of the treatment of tuberculous pericarditis with effusion. Dr. Meltzer will present the history.

Dr. Saul Meltzer: This is the first admission of a 44-year-old Negro man who had been treated during the past year by his family physician for heart disease with congestive failure. He was placed on a salt-poor diet and received an occasional injection of Mercuhydrin. His only complaint was dyspnea on exertion which had increased over the past few months. There was no history of syphilis, diabetes, hypertension, or coronary occlusion. He was in the United States Army during World War II and served in the Philippines, New Guinea, Okinawa, and Japan. He was born in Kentucky. He drank excessive amounts of alcohol on week ends. In 1946 he was admitted to Kings County Hospital for amputation of his left leg following an accident. At that time his blood pressure was 130/90 and his blood serologic test was negative. Two months later he was readmitted to the same hospital with posttransfusion jaundice from which he recovered uneventfully.

In 1951, a chest x-ray showed no abnormality. This was taken at a local health center when his sister-in-law was found to have pulmonary tuberculosis. However, he did not live at his sister-in-law's house.

Physical Examination.—On Oct. 26, 1955, examination revealed a chronically ill male who was dyspneic but not orthopneic. Upon right upper quadrant pressure the neck veins were slightly distended. The heart was enlarged to the right and left. An auricular sound and third heart sound were heard. P_2 was greater than A_2. There were no murmurs. A few fine, moist râles were heard at the left lung base. The liver was felt three fingerbreadths below the right

This is the recording of one of the weekly Medical Conferences held at the Jewish Chronic Disease Hospital of Brooklyn.

costal margin and was not tender. There was no peripheral edema. Fluoroscopy revealed marked globular enlargement of the heart without blunting of the costophrenic angles. The amplitudes of pulsations were very small. Venous pressure was 12.0 cm. with an inspiratory rise of 0.5 cm. Upon right upper quadrant pressure it rose to 15.5 cm. The circulation time arm to lung (ether) was 6 seconds and arm to tongue (Decholin) 14 seconds.

Course in the Hospital.—On October 28, a pericardial aspiration through a xiphoid approach was carried out, and 950 c.c. of turbid, yellow fluid was obtained. Two hundred cubic centimeters of air was injected into the pericardial cavity. Analysis of the fluid revealed that no cells were present. The specific gravity was 1.016 and the total protein 5.98 Gm. per cent. On the following day, the patient complained of pain upon inspiration at the site of aspiration. His temperature rose to 101° F. Fluoroscopy revealed no pleural effusion. The pain and fever continued, and on October 31 there was bilateral dullness over both lung fields posterioly with bronchial breathing and egophony. A pleural rub was heard over the right cardiac border and in the left axilla. The blood pressure did not change and there was no evidence of tamponade. A chest x-ray revealed considerable fluid in the left pleural cavity and minimal clouding of the right costophrenic sinus. The pericardial fluid persisted. The electrocardiogram showed RS-T elevation in the left precordial leads and in Leads aV_F, II, and III. It was thus felt that, twelve hours after the diagnostic tap, the patient had developed an acute exacerbation of his pericarditis and in addition a bilateral pleuritis, despite the administration of streptomycin, isoniazid, and penicillin begun on the day of the pericardial aspiration.

On November 2, a left thoracentesis was done, with removal of 400 c.c. of yellow, thin, turbid fluid from the pleural cavity. Paracentesis of the pericardial sac with removal of 350 c.c. of yellow, turbid fluid was also done because of an enlarging, tender liver.

The pleural fluid contained 1,670 white blood cells per cubic millimeter, with a differential count of 74 per cent polymorphonuclears and 26 per cent lymphocytes. The specific gravity was 1.024.

Culture of the fluids showed no growth of ordinary pathogens or of tubercle bacilli.

On November 4, because of further enlargement and tenderness of the liver, 500 c.c. of serosanguineous fluid was again withdrawn from the pericardial sac.

Laboratory Data.—The hemoglobin was 13.5 Gm. per cent. The white cell count was 7,300 with 61 per cent polymorphonuclears, 29 per cent lymphocytes, 2 per cent monocytes, and 8 per cent eosinophils. The white cell count rose to 15,000 with 85 per cent polymorphonuclears, after the exacerbation of the pericarditis-pleuritis. The blood sedimentation rate was 25 mm. per hour and the blood fibrinogen concentration 291 mg. per cent. There was 1 to 2 plus albuminuria and 6 to 8 white cells per high-power field. The chemical determinations of the blood were all normal except for a low normal cholesterol of 177 mg. per cent. The pericardial fluid was yellow and turbid with a total protein of 5.9 Gm. per cent.

DR. MARTIN G. GOLDNER: The radiologic findings will be presented by Dr. Brenner.

DR. SEYMOUR BRENNER: The first films on this patient were taken on Oct. 11, 1955. In the posteroanterior projection (Fig. 1) a uniform gross enlargement of the cardiac silhouette can be noted which appears to include both sides of the heart. One also notices that the lung fields are grossly clear. There is no evidence of either pleural effusion, pleural thickening, or increase in the bronchovascular markings in either lung field. A Bucky posteroanterior film with barium in the

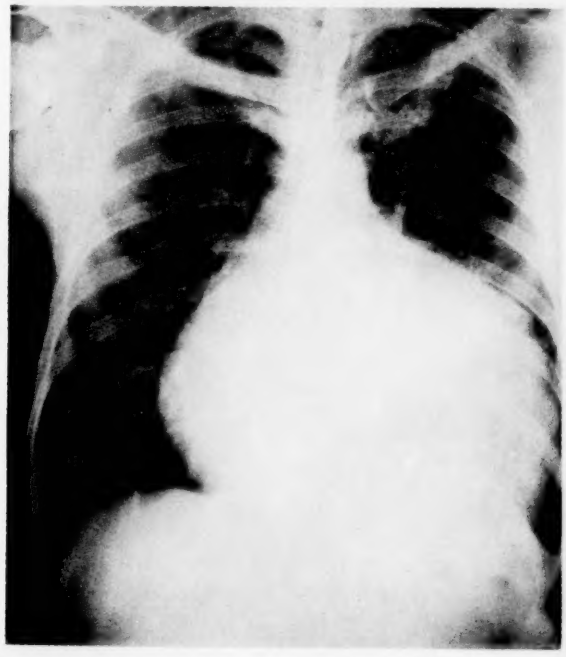

Fig. 1.—Gross enlargement of the cardiac silhouette.

esophagus reveals an essentially normal course of the esophagus. No real displacement by an enlarged left auricle can be seen. No calcifications are present in the regions of the mitral and aortic valves, and the cardiophrenic angles are well maintained. Oblique films with barium-filled esophagus again show no significant displacement of the esophagus by an enlarged left auricle. In the left oblique view, which is more lateral than oblique, we saw what appeared to be some fullness of the posterior border of the heart, which in this projection is made up predominantly of the left ventricle. A kymographic study of the heart (Fig. 2) showed absent or diminished pulsations in the region of the left ventricle, while some pulsations were seen in the region of the aortic arch and aortic knob. Ordinarily the left ventricle should show the most prominent pulsations. On the basis of these first films one can reach several conclusions: there is a grossly enlarged heart; the lung fields are essentially clear, and there is no evidence of chronic or acute cardiac decompensation; there is no evidence of pleural effusion; there is no evidence of displacement of the esophagus by chamber enlargement, particularly of the left auricle; the cardiophrenic angles are well

maintained; finally, there are diminished pulsations in the region of the left ventricle as well as in the right border of the heart with a little more prominent pulsation in the aorta. All this is indicative of pericardial effusion.

Fig. 2.—Kymogram showing diminished to absent pulsations of the left border.

The next films (Fig. 3) are taken with the patient in the lateral recumbent positions and give an excellent demonstration of the positional changes in the pericardial sac filled with fluid. In the right lateral recumbent view, (Fig. 3, *A*) the fluid in the pericardial sac is displaced by gravity so that the cardiac shadow now extends to the thoracic cage. When the patient is put in the opposite recumbent position, there is now lung tissue noted between the cardiac silhouette and the thoracic cage. In a later film (Fig. 4) we also have radiologic evidence that air entered the pericardial sac after the removal of the fluid. There is now an air-fluid level and the pericardium appears slightly thickened. The film taken two days later shows that fluid has reaccumulated, the air has been absorbed, and the air-fluid level has disappeared, but there is fluid in the left lung field. This is the patient's status at the present time.

DR. IRVING G. KROOP: When the patient presented himself, the differential diagnosis was that of an enlarged heart with no history of heart disease. It was surprising that the extent of enlargement of the cardiac silhouette was completely out of proportion to the symptoms. The only complaint of the patient was dyspnea on exertion. Furthermore, the circulation times were normal, which was again out of keeping with the degree of cardiac enlargement. With the minimal pulsations of the left border on fluoroscopy, the diagnosis of pericardial effusion

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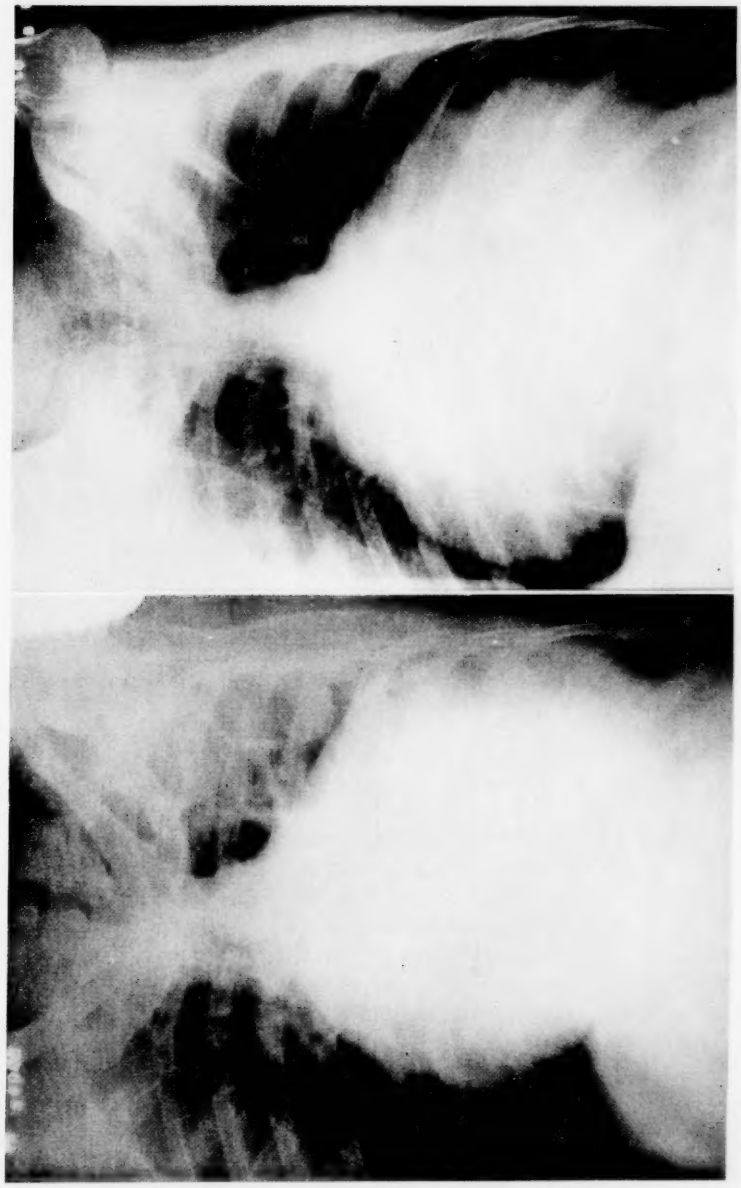

B.

A.

Fig. 3.—Lateral recumbent views: *A*, left side down; *B*, left side up. Note shift of fluid in pericardial sac.

was made. Cardiac catheterization was done in order to see what degree of disturbed cardiac function existed as result of the massive pericardial effusion. I will now discuss the significant cardiac catheterization data. It is important to remember that the patient has only one leg, that he was very difficult to exercise, and that the catheterization could not be done under basal conditions because the patient was apprehensive about the procedure. The data do not represent a true basal state. This man's cardiac output is 6.84 liters per minute per

Fig. 4.—Air-fluid level in pericardial sac.

square meter (Table I). This value is a little above the average normal, but the patient was not in a basal state. I would have expected his cardiac output to be even higher. In fact, his heart rate at the time was 100 per minute, which makes his stroke volume approximately 68 c.c. The normal stroke volume is about 80 c.c. Therefore the patient does have a restriction of stroke output. The cardiac index is 3.7 liters per minute, which again, if a basal state were maintained, would be a relatively high-normal value; but I think this represents a lower value than might be expected if a normal individual were as apprehensive as he was. The pulmonary artery pressure was slightly elevated, 37 systolic over 12 diastolic, with a mean of 23, all in millimeters of mercury (Table II). His "wedge" pressure was high normal, 12 mm. Hg, and the right ventricular pressure was 37/8. The end diastolic pressure of 8 mm. represents an elevation. The mean right atrial pressure was increased to 13 mm. Hg, which goes along with the elevated antecubital venous pressure as determined clinically. These figures, therefore, are those of an individual who, as the result of his chronic cardiac tamponade, has a slight elevation of the pressure in the pulmonary artery and

in the right ventricle, and an inability to empty the right ventricle completely. The high normal pulmonary capillary wedge pressure is indicative of minimal left heart restriction. The fact that all the intracardiac pressures are slightly elevated is indicative of the inability of this heart to fill or empty completely. There is some disturbance in cardiac function, but again not very marked in relationship to the tremendous cardiac silhouette. This is characteristic of restrictive pericarditis due to pericardial effusion where the main defect is not only restriction of filling but also of emptying.

TABLE I. CARDIAC OUTPUT

O_2 Consumption:	170 c.c./min./M.^{2}
A-V Difference:	4.6 c.c./100 c.c. blood
Cardiac Output:	6.84 L./min./M.^{2}
BSA:	1.85 M.^{2}
Cardiac Index:	3.7 L./min.

TABLE II. INTRACARDIAC PRESSURES (MM. HG)

		MEAN
Pulmonary artery	37/12	23
Pulmonary capillary ("Wedge")	—	12
Right ventricle	37/8	—
Right atrium	—	13

When tapping the pericardial sac we measured the intrapericardial pressure before and after removal of 500 c.c. of fluid. The mean positive pressure was 7 mm. Hg before tapping. The normal pressure in the pericardium should be negative or zero, very similar to the intrathoracic or intrapleural pressure. After removal of the fluid, the pressure dropped to a mean of 2.5 mm. Hg. This procedure relieved the patient's tachycardia and he felt very much better. Because cardiac function had adapted itself for a whole year to over 2,500 c.c. of fluid in the pericardial sac, the patient suffered only from dyspnea. The removal of 500 c.c. of this fluid decreased the pericardial pressure and produced symptomatic relief.

Pericardial effusion of considerable amount may be encountered in rheumatic fever, uremia, neoplasia, tuberculosis, idiopathic pericarditis, beriberi, myxedema, and congestive heart failure. The one-year duration of the effusion without clinical evidence of rheumatic activity, primary myocardial or valvular heart disease, uremia, carcinoma, beriberi, or myxedema narrows the etiology down to either chronic idiopathic pericarditis with effusion or tuberculous pericarditis. From the therapeutic standpoint and from a consideration of the relative frequency of the two, the most likely etiology is tuberculosis.

The patient was therefore placed on antituberculous therapy on the day he was tapped. However, twelve hours later, he had an exacerbation of pleuritis-pericarditis. Despite treatment with streptomycin and isoniazid, the fever has

continued for two weeks and the pericardial fluid remains. The questions arise whether it is too early to expect a therapeutic effect, whether we should use other antibiotics, and particularly if and when pericardiectomy should be performed in this patient to prevent future constriction and free his heart from the existent one.

DR. MARTIN G. GOLDNER: Dr. Kroop, would you say a word about the further clinical application of the numerous data on cardiac function which you have presented?

DR. IRVING G. KROOP: The preoperative intracardiac pressures and cardiac output can serve as a base line for evaluating the operative result. The release of the restriction by the surgeon should decrease the pressures toward normal and increase the cardiac output, particularly after exercise. A postoperative cardiac catheterization will settle any question about the degree of residual restriction, if any such question should arise.

DR. MARTIN G. GOLDNER: Dr. Crastnopol, will you give us the surgeon's viewpoint regarding this problem?

DR. PHILIP CRASTNOPOL: The diagnosis of tuberculous pericarditis is one that may be notoriously difficult to make. At the time of operative intervention or autopsy, no distinct tubercles may be found on the parietal or visceral epicardium. It is therefore not unusual that, in this case, we do not have bacteriologic evidence of an acute tuberculous pericarditis. My remarks will be confined to the surgical therapy of tuberculous pericarditis with effusion. Several years ago, Holman[1] introduced a new concept of successful therapy in acute tuberculous pericarditis. He reported several patients who were operated upon in the acute stage under antibiotic control. There are advantages in operation during the acute stage. The pericardium does not have the opportunity to develop the degree of thickening, adherence, and calcification that it will when the process is permitted to extend over a longer period of time. The operation is a simple one, necessitating merely the removal of a loose, flapping envelope around the heart. That is something which can be readily done without any great degree of risk to the patient. In line with this newer concept, Mannix and Dennis[2] of the State University Medical School at Brooklyn, New York, have recently reported another series of patients who have had pericardiectomy for chronic pericardial effusion. The removal of the pericardial sac enables the pericardial fluid to drain freely into the left pleural space and then by tube to an underwater drainage bottle. I recommend pericardiectomy after this patient has had antibiotic therapy, which I think should also include para-amino-salicylic acid.

Immediate surgery with drainage of the left pleural cavity would also prevent a constrictive pleural reaction. If a thickened pleura were found, the lung could then be decorticated. The one danger of surgery in acute tuberculous pericarditis is the possibility of spread, with miliary seeding of other viscera including the meninges. Adequate antibiotic therapy minimizes this risk. Therefore I feel that this patient should be subjected to pericardiectomy and decortication of the left lung if necessary.

It is interesting to note that the exacerbation of the pericarditis and the bilateral pleuritis with effusion occurred following the pericardial tap. One would

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not expect one or two days' treatment with streptomycin and isoniazid to prevent reactivation. Usually, it takes time before the beneficial effect of antituberculous therapy is achieved. Still the exacerbation of infection might have been coincidental and unrelated to the pericardial tap.

DR. MARTIN G. GOLDNER: We have a few guests here who are experts in this field. Dr. Crastnopol has presented the surgical indication and procedure and has stressed preoperative antibiotic therapy. May I call now on Dr. Lyons, Associate Professor of Medicine, State University of New York, and Chief of the University Chest Service at Kings County Hospital, to give us his opinion?

DR. HAROLD LYONS: I think we ought to presume that this illness is tuberculous because of its prolonged nature and because there is no clue to any other disease. I doubt that this could be a rheumatic pericarditis although this process may be extensive and massive. We presume, from what Dr. Kroop said, that this effusion has existed for about a year, and I doubt whether a rheumatic pericarditis could exist for one year without some other sign of rheumatic activity. This patient presents many features of the kind of constrictive pericarditis that we see at Kings County Hospital. The patients are usually alcoholics who come in because of ascites and edema of the legs. Many of them have been called cirrhotics and they go on with that diagnosis for a long time. In addition to the alcoholic history, we have found some other perplexing problems, such as associated myocarditis and endocardial fibroelastosis. In one patient with all the typical findings of constrictive pericarditis, endocardial fibroelastosis was found at operation.

Myocarditis of various sorts can give the same characteristic feature at cardiac catheterization—the early diastolic dip in the ventricular pressure curve as is seen in restrictive pericarditis. Amyloid and fibrous myocarditis are good examples. We also had one case where this was seen without disease of the pericardium, heart, or endocardium; this was in a patient with pectus excavatum.

For the treatment of this patient, I too would use antituberculous therapy. The best drug that can be used in such a case is one that has great diffusibility, i.e., isonicotinic hydrazide. However, after such a prolonged illness one cannot expect an immediate result! One should hope to have a result within two weeks, but some tuberculous patients need still more time. Sometimes it takes as long as four to eight weeks before one sees a response. Some people advocate the use of triple therapy—streptomycin, INH, and PAS. I am not yet convinced that this is any more beneficial than the combination of two of these agents. In addition, when one uses all three drugs one has already fired all the ammunition and has then subjected the patient to the possibility of more toxic reactions.

Now we come to the question of whether operation is necessary at this moment. I agree with Dr. Crastnopol's attitude. We have done this procedure on many patients. The criteria for surgery included poor response to antibiotic therapy, large pericardial effusion, and congestive failure. The patients who were subjected to early operation had a dramatic response. They became afebrile, felt better, and their symptoms disappeared. The patient under discussion has had adequate antibiotic therapy and I feel that pericardiectomy should be performed.

DR. MARTIN G. GOLDNER: We have the presumptive diagnosis of tuberculous pericarditis, and so far our discussants agree that in addition to antituberculous drug therapy, operation should be carried out. I call now on Dr. Whitehead of the United States Public Health Service Hospital at Manhattan Beach, Brooklyn.

DR. ROY E. WHITEHEAD: I have seen a number of cases of tuberculous pericarditis, none quite as extensive as in this patient. A diagnosis of tuberculous pericarditis in this case is probably correct. The fact that the organisms were not found in the fluid does not rule out tuberculosis. Usually there is a miliary involvement on the wall of the sac. Let me emphasize that many of these cases have gotten well without surgery, even before we had chemotherapy. This situation is about the same as tuberculosis pleurisy with effusion. We use chemtherapy routinely and do pleural taps only if the fluid is producing symptoms.

In this case, I would continue treatment with streptomycin and isonicotinic hydrazide for at least two to three months in order to give the antibiotic therapy a fair trial. Surgical intervention would be indicated if there is no improvement by that time. In the meantime, the pericardial sac may be tapped if necessary and even drained. Personally I hesitate before considering surgical intervention in any acute case of tuberculosis, despite antibiotic therapy.

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DR. PHILIP CRASTNOPOL: I would like to add to the discussion in view of what Dr. Whitehead has just said. I think that any pericardial drainage procedure is apt to fail for one or two reasons. First of all, any prolonged drainage of the pericardium is likely to result in secondary infection, resulting in a mixed rather than a simple tuberculous infection. We know how high the mortality is in a mixed tuberculous infection. Second, the pericardium notoriously seals itself off very quickly so that any simple drainage operation is apt to result in drainage of a very localized area with considerable residual fluid in the rest of the pericardial space. I do not think any procedure of that kind should be contemplated. I would certainly be willing to wait another two weeks to see whether we could control the fever. I agree with Dr. Whitehead that there is a great advantage to operating on these patients in a quiescent state, if it can be attained, without prolonging the morbidity over too long a period of time.

DR. ROY E. WHITEHEAD: I do not say that I am opposed to surgery and I agree that this case might eventually have to come to it. In this acute case, however, we would do better to allow the natural processes to take place. If a tuberculous empyema and mixed infection develops, I would not hesitate to use surgical intervention. Apparently, the pericardial and pleural fluid is now serous and there is no evidence that the patient has a mixed infection.

DR. HAROLD LYONS: I think Dr. Whitehead may have misunderstood. We do not treat all our patients by operation. There are patients who do well on antibiotic therapy. However, my experience has been that patients with long-standing effusions, as in this particular case, end with constrictive pericarditis. It is much easier for the surgeon and is a much less extensive operation, with better results, if the patient is operated on during the effusion stage.

DR. SOLOMON SLEPIAN: Can cortisone be used to control the constitutional symptoms now that the patient is receiving antituberculous drugs?

DR. MARTIN G. GOLDNER: I feel cortisone should not be given in any case where there is the remote possibility of tuberculosis. Since the patient is still very ill, I feel that at present we should continue antibiotic therapy in order to control the acute infection. After this is done, pericardiectomy should be performed in order to prevent constrictive pericarditis.

FOLLOW-UP

After continued antibiotic therapy, the patient was subjected to a total pericardiectomy with complete recovery. Operation was performed on Dec. 6, 1955. The parietal pericardium was thickened and chronically inflamed, and there was 300 c.c. of serous fluid in the pericardial space. Many fresh pleuromediastinal adhesions were separated by sharp and blunt dissection. The pericardium overlying the anterior, lateral, and diaphragmatic surfaces of the heart was resected. The patient tolerated the procedure quite well and returned to his room in good condition.

Microscopic examination of the specimen showed hyalinized connective tissue with some acute inflammation. There was no evidence of tuberculosis. Culture and smear of concentrated, macerated pericardium were negative for acid-fast bacilli.

Convalescence was uneventful. Although the heart remained enlarged, the neck veins were not distended and there was no peripheral edema, dyspnea, or orthopnea. The patient was discharged from the hospital on Jan. 17, 1956. Two months after the operative procedure, the patient returned to his job as janitor.

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Editorials

LABORATORY AIDS IN THE DIAGNOSIS OF CARDIAC INFARCTION

In any large number of patients with real or suspected myocardial infarction, there are more than a few cases which puzzle the electrocardiographer. Common events such as the "masking" of infarction by ventricular arrhythmias or conduction disturbances, the occurrence of nonspecific ST and T wave aberrations, and the impossibility of disentangling evidences of fresh necrosis from the relics of older infarction—these constitute some of the everyday experiences of the cardiologist.

Dilemmas of this sort have encouraged a search for auxiliary methods which might assist in the recognition of cardiac infarction. Fever, leukocytosis, and elevation of the erythrocyte sedimentation rate were noted early in the history of recognition of this disease.[1] As useful as these observations can be, their lack of specificity and occasional erratic appearance are well known. Since tissue necrosis is present, it seems not unreasonable to expect some help from new biochemical methods in the detection of circulating tissue debris. Although we are still far from an exact chemical characterization of heart muscle necrosis, the size of the recent literature on this subject attests to the enthusiasm for diagnostic laboratory methods in patients with acute coronary thrombosis.

Now that elaborate new techniques can be brought to the assistance of the cardiologist, attention has been focused on two main types of body chemical alterations in patients with infarction. For example, a whole battery of nonspecific indications of tissue damage, referred to as "acute phase" reactants, may be found in the circulating protein and related serum constituents of patients with fresh myocardial infarction. Elevation of concentration of serum fibrinogen, copper, mucoprotein, cryoglobulins, C-reactive protein, serum complement, changes in electrophoretic patterns, and a fall in serum iron and serum cholinesterase are all described.[2] The great simplicity and accuracy of the method for measuring C-reactive protein has led to the wide use of this determination.[3] However, lack of specificity limits the usefulness of all the measurements in this group.

Other metabolic changes which have been shown to occur in acute infarction do not serve to distinguish this disorder from a variety of other "stressful" conditions. For example, increased protein catabolism, augmentation of urinary coproporphyrin, catecholamine, creatine, glucose, and steroid excretions (all of which are described) seem to be of theoretical rather than practical interest at this time.[4]

To date, the most stimulating approach to a specific biochemical diagnosis of heart muscle damage has been the observation of LaDue, Wroblewski, and Karmen and their co-workers.[5] These investigators, reasoning from previously

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known information indicating abundant quantities of glutamic-oxaloacetic transaminase in heart muscle and having devised a simple spectrophotometric test for its presence in serum, were able to demonstrate that upon death of cardiac muscle the circulating blood became rich in transaminase activity. The enzyme is normally present in small amounts in normal sera, and increases occur within six hours of acute myocardial infarction. Peak levels as high as 2 to 20 times the normal values are reached within twenty-four hours and appear to bear some relation to the mass of muscle which has been infarcted. There is a fairly strong indication that a very high peak level is an ominous prognostic omen. The rapid fall in serum activity results in return to normal levels within three to seven days, dependent, in part, on the height of the peak levels which were previously attained.

Measurement of serum transaminase can be done in most well-equipped hospital and clinical laboratories. Procedures are reasonably standardized and the necessary reagents are commercially available. It is likely that modifications of the technique will make it adaptable to less expensive spectrophotometric apparatus than is now required.

At the moment, no method is available to distinguish transaminase of cardiac muscle origin from enzyme which has leaked from other tissues. Therefore, this test is also "nonspecific." Actually, the highest observed levels are seen in liver disease, and respectable amounts are noted in acute destructive processes involving kidney, pancreas, and skeletal muscle as well. There is reason to hope that the next step in progress may be the development of methods of detecting specific tissue components in circulating blood, whether they be enzyme proteins such as transaminase or some other substance.

In our own experience with the method, we have been aware of possible limitations of this test. Some reservation should be made to the effect that there is insufficient proof that severe ischemia may not result in some leak of enzyme into the blood. Rarely and inexplicably, we have seen proved infarction without an elevation of transaminase activity beyond the normal range. Nonetheless, our own experience has convinced us of the great importance of the method in those very situations where help is most needed: suspected instances of infarction in which atypical or masking electrocardiographic changes are observed. It certainly appears that this biochemical indicator of cardiac muscle dissolution will call attention to many clinical episodes of infarction which have hitherto been only suspected, but not susceptible to rigorous electrocardiographic confirmation. The biochemist may now be preparing to step in where the conservative electrocardiographer has rightly feared to tread—into the shadowy no man's land of "T wave infarction," "subendocardial infarction," and "coronary failure."

One of the most gratifying applications of this test has been to the group of patients with acute benign nonspecific pericarditis. These patients, usually young men, are surrounded with an aura of anxiety and uncertainty often reflected in the attitude of the puzzled physician himself. The transaminase activity is usually quite normal in pericarditis and this is a most reassuring datum. In most patients with angina, acute pulmonary embolism, mediastinal

emphysema, dissecting aneurysm, and a variety of other noncoronary causes of acute chest pain, elevation of transaminase activity is not observed.

If this test or its successors do, indeed, fulfill their original promise, we shall have a more rigorous standard for evaluating difficult electrocardiograms in surviving patients. No one will regret discarding once and for all such weasel words of electrocardiographic interpretation as "damage" and "involvement." In conclusion, we might also predict that chemical diagnosis, by helping to recognize previously overlooked infarction, may contribute both to the welfare of afflicted patients and to a better understanding of the morbidity and natural history of a ubiquitous chronic disease.

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VITAMIN C AND RHEUMATOID ARTHRITIS

Sir Frederick Bartlett is quoted[1] as having said: "The process of bringing together fields or items of knowledge and observation which have hitherto been unrelated is almost always the first step of discovery, especially in biology." A possible relationship between vitamin C and rheumatoid arthritis has long been postulated. A deficiency of this vitamin, as well as the disease process in rheumatoid arthritis, affects connective tissues in dramatic ways. Arthritic and scorbutic individuals frequently present similar symptoms. Are these dependent or independent effects? If the effects are dependent, a much needed opportunity exists for delving into the pathogenesis of the devastating rheumatic diseases.

During the War of the Austrian Succession, in 1747, Surgeon James Lind[2] of the British Navy proved by a controlled experiment aboard ship that the lack of a dietary component was indeed the cause of scurvy; but not until 1930 was a sufficiently concentrated effort made to make the crystalline vitamin available for nutritional and therapeutic use. King[3] relates that his student, Waugh, who first crystallized the vitamin, had been urged by another professor not to work on vitamin C because it was an obviously impossible task. King himself had been advised not to take up a study of vitamins, for the study would have no significance in America, where food supplies are abundant. The weekly production of this vitamin in the United States is presently around ten tons. Yet, we still have practically no specific information as to the biochemical reactions mediated by vitamin C.

The Sub-committee on Mesenchymal Tissues to the National Research Council Committee for Survey on Research on Rheumatic Diseases reported in 1948 in part as follows: "Since the rheumatic diseases are believed to involve primarily derangements of the mesenchymal tissues or their derivatives, research of the most basic character (structure, composition, and function) of these tissues in health and disease is essential for significant advances in the prevention and treatment of this group of diseases." In 1953, Bennett[4] pointed out that the situation had not changed significantly. In 1956, the same holds true. Since vitamin C is known to be an essential factor in the biologic processes of connective tissue formation and repair, the determination of its mechanism of action should receive prominent consideration.

Plasma levels of the vitamin are low in a sufficient number of persons afflicted with rheumatoid arthritis for a question of a cause or effect relationship to be suggested. However, from the clinical viewpoint, the use of vitamin C in the treatment of rheumatoid arthritis has been disappointing. The patient may be helped if he is suffering also from general nutritional deficiency or from certain forms of anemia. But contrary to the dramatic response noted in scurvy, rheumatoid arthritis is not demonstrably improved by therapy with this vitamin. Reports of beneficial effects from the vitamin or from a combination of the vitamin

and steroid therapy have not withstood critical re-evaluation. A lack of success has also attended efforts to determine the function of the vitamin in the adrenal glands, where it is closely associated with ACTH function.

The concept of a direct relationship between vitamin C deficiency and rheumatoid arthritis has not been completely abandoned and, in view of the complexity of these relationships, should not be discarded. The idea lingers that somehow a prolonged period of "subclinical" deficiency of the vitamin might lead to irreversible damage to connective tissues. Is there a benefit to be derived from vitamin C more than the mere prevention of obvious disease? The League of Nations Health Organization recommends a daily intake of 30 mg. of vitamin C for the requirement of a normal human adult. This quantity allows a margin of safety over the 10 mg. amount found to prevent or alleviate symptoms of scurvy in the Sheffield experiment in Britain and in Crandon's experiment in America. The Food and Nutrition Board of the National Research Council, U.S.A., recommends 75 mg. per day. The food habits and economies of the nations, as well as the manner of evaluation, are reflected in these recommendations. It is of interest that those animals which synthesize their own vitamin C maintain their tissues at near saturation levels, a state which would require a daily intake of 75 to 100 mg. for the human adult.

At the present time, much ado is being made of the presumed larger amounts of vitamin C needed under so-called conditions of stress. Consequently, some physicians advocate the administration of large amounts of the vitamin during the course of severe infections or after injuries and in other circumstances involving particularly active metabolism. No injurious effects of the vitamin have been revealed. Yet others caution against continued administration of large amounts of a substance whose action is such a complete mystery.

It is generally presumed that vitamin C affects various enzymes through reactions mediated by its oxidation-reduction potential. Another biologic process, other than connective tissue formation, in which vitamin C is known to be involved is the metabolism of tyrosine. Here, a hydroxylation reaction appears to be involved, but the effect of ascorbic acid may be indirect. Recent work of Axelrod, Udenfriend, and Brodie[5] indicates that vitamin C may also be involved in the detoxification of aromatic compounds through hydroxylation. These observations lead to speculation that a possible hydroxylation reaction may involve the vitamin in the incorporation of hydroxylysine and hydroxyproline into collagen, of which these hydroxy acids are so peculiarly characteristic.

A new approach is timely in the search for the cause of rheumatoid arthritis. One of the needs for guidance in this search is more knowledge of the connective tissue components and their method of formation and repair. It is reasonable to expect that a determination of the mode of action of vitamin C in this area will at least provide much needed new leads for further work.

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ACROSS-THE-COUNTER HYPNOTICS: BOON, HAZARD, OR FRAUD?

The consumer who wants to buy something purported to help him sleep has no difficulty in doing so today—and he doesn't need a prescription. Radio and newspaper advertisements describe the benefits of a host of invitingly named drugs. Over-the-counter sales of Sleep-Eze, Sominex, Nite Cap, Nytol, Quietabs, Safe-Sleep, Restryl, Somnesia, Rest-Rite, Drowze, etc., etc., are reported as brisk. What *are* these drugs? How good are they? How safe are they?

In general, these products contain an antihistamine preparation. In the overwhelming majority of cases, the antihistamine is methapyrilene hydrochloride (Histadyl, Thenylene), 25 mg. per capsule. Some contain, instead, another antihistamine, pyrilamine maleate (Neo-Antergan). In addition, some of these preparations include other substances, such as scopolamine aminoxide hydrobromide in dosages of approximately 0.15 mg. per capsule. Presumably these drugs have come to be promoted as hypnotics because of the drowsiness observed as a side effect attendant on their use in the treatment of allergic disorders and in the prevention of motion sickness.

How effective are the preparations? No one really knows. Every physician in the country is aware of the ability of most antihistamines, given in sufficient dosage, to affect the central nervous system—sometimes with resultant stimulation, usually with sedation, occasionally with both. The usefulness of the "hypnotics" named in the introductory paragraph could be fairly easily evaluated in a controlled clinical trial, but unfortunately definitive data are not yet to be had. One study on methapyrilene has been reported,[1] and the description of the protocol followed seems adequate enough. It is slightly disturbing, however, when we are told that the results were analyzed by four different statistical procedures, and a method finally selected on the basis of being most "sensitive in the determination of differences among the compounds." Even in the data presented (presumably the most clear-cut analysis), there are unhappy discrepancies between subjective (patient) and objective (nurse) reports, and the impression one gets is that 50 mg. of methapyrilene was perhaps a weak hypnotic, of the order of potency of 0.1 Gm. or less of phenobarbital. (The latter dose of phenobarbital has recently been reported as a relatively inefficient hypnotic.[2])

How safe are these capsules? A standard pharmacologic text[3] lists a host of untoward reactions to antihistamines—excessive sedation, dizziness, tinnitus, lassitude, incoordination, fatigue, blurred vision, euphoria, nervousness, insomnia, tremors, anorexia, nausea, vomiting, epigastric distress, constipation, diarrhea, dryness of the mouth, urinary frequency, dysuria, palpitation, hypotension, headache, tightness in the chest, tingling, heaviness, weakness of the hands, dermatitis, leukopenia, agranulocytosis, and hyperpyrexia. Acute poisoning from antihistamines has occurred in both children and adults. Methapyrilene is no exception to the above categorization of antihistamines as potentially toxic agents. Accidental ingestion of 800 mg. of methapyrilene by a

20-month-old child resulted in cyanosis, unconsciousness, convulsions, and cardiorespiratory depression.[4] The fatal poisoning of a healthy girl 16 months of age from accidental ingestion of 100 mg. of methapyrilene has been reported.[5] A case of suicide with this agent is on record.[6] One must bear in mind, however, that side effects of many types, including death, occur after many drugs, including aspirin; and only the unpleasantly high incidence of nasty side effects (taking into account the relative severity of the condition being treated) is ordinarily an indictment of a drug.

What of scopolamine aminoxide hydrobromide? Again we have good reason for believing that considerable toxicity is achievable with certain doses of this drug. One milligram three times a day has been found to produce a high incidence of blurred vision and dry mouth. Double this dose produced, in addition, nightmares, hallucinations, and mania.[7] These unpleasant symptoms occurred within twenty-four to thirty-six hours and lasted a day or more.

Why can these nonbarbiturates be bought so easily? The antihistamines were originally considered as new drugs, restricted to prescription sale. After a period of time, data were accumulated on the relative safety of antihistamines, and they were approved for over-the-counter sale in certain dose ranges and with "adequate directions for use and warnings against misuse." (This does not apply to all antihistamines. The barbiturates are restricted by law to prescription sale.)

Is there reason for believing that Sleep-Eze, Nite Cap, etc., are much *safer* hypnotics than barbiturates? Usual doses of pentobarbital or secobarbital can certainly be taken by many patients nightly for long periods of time without the development of significant physical dependence or disabling side effects. That certain predisposed individuals abuse barbiturates and either attempt suicide with them or become barbiturate addicts is true; but addicts will abuse even antihistamines on occasion,[8] and it is obvious that suicide can be achieved with antihistamines. Of interest is the fact that, in Canada, "it is not considered in the interests of public health for antihistaminic drugs to be advertised to the general public as sedatives."[9]

Is there reason for suspecting the new preparations to be perhaps safe, but essentially *inactive*, in the prescribed doses, so that the advertising claims of the drug manufacturers are actually fraudulent? Some think so, but again we don't know.

Is it possible that some antihistamines (minus scopolamine!) might in adequate dosage prove useful as sleeping medications? It is quite possible. There must be a fair number of patients who first stumbled on the sedative effects of certain antihistamines upon taking the drugs for hay fever or some other histaminic grievance, and who have continued to take the drugs as sedatives or hypnotics. An acquaintance of mine has now been taking Benadryl nightly for over two years; he sleeps well and has apparently suffered no untoward effects. One would like to see a number of antihistamines compared with a first-rate hypnotic like pentobarbital or secobarbital, in a controlled experiment, to determine both relative efficacy and relative toxicity.

It would be amusing (although admittedly unlikely) if it turned out that there was a larger market for Pyribenzamine or Benadryl or Dramamine as

hypnotics than as antihistamines. Particularly delightful to watch would be a drug house sales manager describing the same drug as "a potent sleep-producer" in one advertisement, and "a powerful anti-allergy drug with minimal side effects" in another.

It is unfortunate that the Food and Drug Administration cannot take regulatory action against a drug whose efficacy for the conditions for which it is offered has not been demonstrated. Adequate *toxicity* data are required from manfacturers before introducing new drugs; similar requirements as to *effectiveness* should be included in our federal statute. It appears to be an accepted fact that toxicity and efficacy cannot each be considered separately, *in vacuo* as it were. Is it such an horrendous leap, therefore, from the present position to one where respectable, reliable evidence about a drug's therapeutic potency must be provided by the manufacturer before a compound is released? Must we put the onus of proof on the Food and Drug Administration, insisting that they build up a strong case *against* a worthless drug already on the market, in order to restrain unprincipled advertising?

In summary, one can say that the practicing physician ought to know: (1) that across-the-counter "hypnotics" are not only available to consumers, but popular with them; (2) that they are antihistamine preparations (predominantly methapyrilene), in some instances with scopolamine or other substances added; (3) that these preparations, if taken in sufficient quantity, can be dangerous, but that there is apparently little reason for believing that the prescribed dosage will prove toxic for most adults; (4) that there is a dearth of information on how effective these agents are. Adopting a rational stand on their over-all use by patients will remain a difficult problem for physicians until such time as more data become available.

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Book Reviews

CIBA FOUNDATION SYMPOSIUM ON EXPERIMENTAL TUBERCULOSIS, BACILLUS AND HOST. ADDENDUM ON EXPERIMENTAL LEPROSY. Editors for the Ciba Foundation: G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch., and Margaret P. Cameron, M.A., A.B.L.S., assisted by Cecilia M. O'Connor, B.Sc. Pp. 396, with 69 figures; indexed. Boston, 1955, Little, Brown and Company. Price $9.00.

This volume is an account of the proceedings of a Ciba Symposium held October, 1954, in London. Anyone who has had the privilege to attend such a symposium knows in what an atmosphere the meetings are held. This book reproduces, as much as is possible in written form, the informal exchange of ideas and criticisms during the symposium. Above all, the collected papers show that research in tuberculosis has reached a certain stage of maturity, a phase in which it has become possible to separate and analyze certain factors underlying the interactions between the host and the tubercle bacillus. It is not implied that answers to the basic questions have been found; it is only suggested that techniques and ideas have been developed which promise to yield new and valuable information about the fundamental problems of the tuberculous infection. It is impossible to mention all the contributions collected in this book, but a few topics will be discussed briefly here.

One group of presentations is mainly concerned with the components of the tubercle bacillus and their serologic reactions with immune sera. These components are mainly proteins and polysaccharides (Stacey, and Iland and Peacock) and various fractions of culture filtrates of tubercle bacilli (Boyden and Sorkin). In particular, the chemistry of fractions containing mycolic acid has been considerably advanced (Lederer). This is of great importance because such fractions have been found to contribute to the ability of tubercle bacilli to establish an infection (the so-called cord-factor) (Bloch) and also to exert a certain toxic effect upon tissues. Other fractions composed in part of mycolic acid, such as the wax D, induce granuloma formation in the tissues (Ungar, and White) and play a role in the induction of delayed hypersensitivity (Raffel). The potentiality of these fractions as immunizing antigens is still disputed (Suter).

More complex and more mysterious is the nature of the response of the tissues to the presence of tubercle bacilli and the consequences of this response for the subsequent course of infection. Even in a primarily chronic infection the early tissue reaction seems of consequence (Miles). Normal tissues contain substances such as spermine and basic peptides, which are inimical to the tubercle bacillus. Their actual activity in suppressing bacterial multiplication in vivo is still obscure (Hirsch). Similarly the nature of the immune response, of increased resistance to infection, is unsolved. Cells seem to be involved (Suter), since tubercle bacilli are intracellular parasites (Brieger), and no circulating antibody has so far been demonstrated to contribute to immunity to infection (Raffel). The question of whether tubercle bacilli have to multiply or not in order to induce immunity in the host is a timely one (Bloch) because important practical decisions depend on this answer.

The reaction of the host to tubercle bacilli is both local and systemic. The endocrine apparatus plays a key role in the host's reaction to infection (Lurie and Zappasodi). There are also biochemical alterations in tissues not directly infected with tubercle bacilli, such as the kidney in the guinea pig. Kidneys of infected guinea pigs have reduced succinic dehydrogenase activity, and it seems as if this alteration depends on the lack of a certain cofactor (Martin). This biochemical lesion might be of great importance in the understanding of the tuberculous infection.

A very detailed description of the alteration of the tissue reaction as a consequence of chemotherapy is also included (Canetti). An increase in the specific cellular metaplasia is noted with conspicuous absence of tubercle bacilli within thosel esions. The observation that certain surface

active agents alter the host-parasite relationship may prove to be of great consequence. Thus, substance inactive in vitro, Triton WR 1339, increases the resistance of experimental animals to infection with tubercle bacilli by reducing the ability of the latter to multiply within the monocytes of the host. An alteration of the bacterial surface by the agent (which becomes localized within phagocytes) may well be involved (Hart and Reese).

A number of papers deal with the nature of the tissue reaction to the leprosy bacillus. There are numerous similarities with the tuberculous reaction (Lurie). Thus, circulating antibodies do not seem involved in resistance to infection, sensitization is an obligatory consequence of infection, and the cellular reaction seems to be the basis for the emergence of immunity (Lowe).

This brief summary can only indicate the various lines of approach to the problems of tuberculosis. More and interesting results can be expected in the future.

Emanuel Suter

EXCITABILITY OF THE HEART. By Chandler McC. Brooks, Ph.D., Brian F. Hoffman, M.D., E. E. Suckling, M.Sc., M.E.E., and Oscar Orias, M.D. Introduction by Carl J. Wiggers, M.D. Pp. 388, with 86 illustrations; indexed. New York, 1955, Grune & Stratton, Inc. Price $6.50.

This excellent monograph, written in a singularly lucid style, should be of great value to the physician as well as to the physiologist.

The first five chapters discuss the fundamental aspects of the excitatory process as evidenced from the most recent investigations of excitability in single myocardial cells and in intact hearts. Most of the material included here comes from the authors' own researches which, since 1948, have been outstanding in the field of cardiac physiology. The information, however, is also generously documented with the results of other investigators. The third chapter contains a detailed description of the techniques and methods used in the study of intact hearts and single fibers. This chapter should prove especially useful to anyone who is actively engaged in cardiac research.

The remaining chapters deal with such important subjects as fibrillation, cardiac reactions to heat and cold, autonomic and chemical mediation of cardiac activity, inorganic ions and cardiac excitability, and the relationship between the mechanical and electrical responses of the heart. All of these topics are discussed with respect to the cellular physiology of the excitatory process as elucidated in the first five chapters.

The format of this monograph is exceptionally well constructed. The print is good, the photographic reproductions are adequate, and the figure legends are well prepared. In addition to a short initial résumé, there is an excellent summary included at the end of each chapter. The final chapter, moreover, consists of a general summary and conclusions. A well-chosen list of references, both classical and general, is included at the end of each chapter. Much of the literature cited is extraordinarily recent. The rather complex theories of cellular membrane phenomena associated with excitation are presented clearly without sacrificing accuracy of detail. This monograph will undoubtedly become a classic in its field as predicted by C. J. Wiggers in his introduction to the work.

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